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WITH THE HELP OF

H. C. CAMERON, M.D., F.R.C.P.
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C. MAX PAGE, D.S.O., M.S., F.R.C.S.
LEONARD G. PARSONS, M.D., F.R.C.P.
G. F. STILL, M.D., F.R.C.P.
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PATENT DUCTUS ARTERIOSUS

BY

D. C. MUIR, M.D., M.R.C.P.,

and

J. W. BROWN, M.D., M.R.C.P.

The impression that has been gathered from a perusal of the available literature is that a patent ductus arteriosus as a sole abnormality is comparatively rare. In Abbott's[1] collected series of 850 cases there were but 73, and in Laubry and Pezzi's[2] well-known work the lesion is said to be rare. Recently Perry[3] in a review of congenital heart lesions in Bristol school children found, amongst 121 cases, 8 instances (6 per cent.) of patent ductus arteriosus. In our own series of 88 cases of congenital heart disease occurring for the most part in school children, we find no less than 20 cases or 23 per cent. of the total to have signs which suggest a patent ductus arteriosus as the sole abnormality.

Much has been written with regard to this abnormality, for where it has been discovered it has usually been well studied. Perhaps it is the most completely investigated lesion in congenital cardiac pathology.

Symptoms.—It has been said that subjects with a patent ductus arteriosus are generally slightly built, somewhat under-developed and anæmic. A wax-like pallor has been recorded as present and characteristic, and this has been attributed to a hypoplasia of the aorta with consequent depletion of the arterial system. All are agreed that there are rarely any symptoms. Such symptoms as have occurred are those of hyperpnœa on exertion and palpitation. Cyanosis is usually absent, and when it has occurred it has been in relation to exertion or to pulmonary infection, and thus in the latter case follows the lines of the ' cyanose tardive ' described by the French. Epileptiform convulsions may occur in patients with congenital heart disease with lesions that permit venous shunting. This is especially so in infants where such an act as sucking raises the pressure in the pulmonary artery above that in the aorta. In 2 cases of patent ductus arteriosus recorded by Shirley Smith[4] such fits occurred and were associated with cyanosis. More recently Leech[5] has collected similar cases.

Physical signs.—The characteristic physical sign is a long rough murmur best heard in the first and second left interspaces, though sometimes a little lower, close to the sternum. The character of the murmur varies with the age of the patient. In infancy when the patent duct is a straight tube the murmur may be indistinguishable from that caused by a septal defect. When the pulmonary artery becomes dilated in later childhood the bruit takes on its

continuous character. At just what age this may occur it is difficult to say. The murmur may be systolic in time but more often it is continuous, being best heard in systole, when it is reinforced, and waning in diastole. This continuous murmur, which was first described by Gibson[6], is absolutely pathognomonic, and has been variously described as continuous, churning, humming, rolling thunder, machinery, tunnel-like or sawing. It is usually best heard in the second left intercostal space close to the sternum: occasionally better over the third left interspace. The murmur increases on inspiration and sometimes the continuous element of the murmur is best appreciated with the subject erect. The systolic element may be heard at the apex, towards the left axilla, along the left border of the sternum, and under the clavicle. At times it may be heard in the left carotid, and not infrequently in the left mid- and infra-scapular region. In the latter situation it has been attributed to a narrowing of the aorta at the site of the ductus. A diastolic bruit may be present and heard along the left border of the sternum. This has been attributed by Laubry and Pezzi[2] to dilatation of the pulmonary artery, or it may be due to aortic incompetence. The possibility that aortic reflux, if present, may be the result of infection of the aortic valves should not be forgotten. In cases where the communication is large there is lively arterial pulsation in the neck accompanied by a low diastolic pressure and this may lead to further confusion with aortic regurgitation. The pulmonary second sound is accentuated or reduplicated. This sign may be easily overlooked unless it is sought for below the site of maximum intensity of the murmur. Although this sign has a certain value in the differential diagnosis it must be interpreted with caution, as an accentuated pulmonary second sound is a common finding in children. Accompanying the murmur may be a thrill which is systolic, continuous or diastolic in time, and may be diffuse, or localized to the base, with maximum intensity in the second left interspace, or at a site corresponding with the maximum intensity of the bruit. In Abbott's 84 collected cases it was present in 23; in 9 continuous, in 11 systolic and in 3 diastolic. A systolic thrill would appear to be more frequent than a continuous thrill. Its absence has been interpreted as indicating that the communication is large. Dilatation of the pulmonary artery is almost invariably present, because the flow of blood is from the aorta into the pulmonary artery, although under certain conditions the flow may be in an opposite direction (Holman[8]). It is shown by Gerhardt's dullness, a ribbon-like area of dullness in the second and third left spaces close to the sternum. This is not always clinically appreciable in children, but can almost always be detected in adults. Confirmation may be obtained by the use of the X-rays, when the cardiac silhouette characteristic of the lesion may be discovered. Gerhardt in addition described visible systolic pulsation in the second left space, but this sign cannot always be elicited despite the presence of dullness.

Certain arterial phenomena have been recorded. There is no change in the systolic pressure but the diastolic pressure may be lowered, giving rise to an arterial dance, and confusion with aortic incompetence. The pulses

may be unequal, the left being smaller than the right and delayed in comparison with the right. A difference in amplitude between the femoral and radial pulses has been emphasized by Laubry[7], and when this is present it is significative of some slight stenosis of the aorta, perhaps insufficient to cause a dorsal systolic bruit. These arterial changes are best detected by polygraphic methods, and when present they are striking.

The pulsus paradoxus, said to occur in this condition (F. Franck), is inconstant and not a striking feature in most recorded cases. The blood pressure may be lower in the left arm than in the right. Paralysis of the left vocal cord due to pressure on the recurrent nerve is a rare, but valuable sign.

Radiological examination.—This is always of the greatest importance in assisting the diagnosis and in confirmation of clinical findings. The heart should be observed with rays as nearly parallel as possible, and the right oblique view should be used in addition to a frontal examination. Sometimes there is apparently no change in the cardiac silhouette in the frontal position in children, but in the right oblique position dilatation of the pulmonary artery can be seen. Sometimes on the screen the appearances, despite obvious physical signs, are normal. More often there is alteration in the pulmonary arc of the left cardiac border, the middle arc being prominent, rounded, and bulging, and in some cases almost hemispherical. This is even better seen in the oblique view, and corresponds to the dilatation of the trunk of the pulmonary artery which is a common but not essential accompaniment of a patent ductus arteriosus. In cases where the pulmonary arc is enlarged there is also enlargement of the right cavities of the heart. This prominence of the pulmonary arc has been called the X-ray cap of Zinn. There is rarely any increase in the left side of the heart unless there is some added complication such as co-arctation of the aorta or aortic reflux.

Electrocardiographic results.—These are most frequently physiological, although there may be increased amplitude of the QRS complexes. There is nothing in the electrocardiogram that is in any way diagnostic of the condition.

Diagnosis.—As criteria in diagnosis we have accepted the following physical signs as being the most essential:—

1. The presence of a continuous or machinery murmur, maximum in the second left interspace close to the sternum.
2. A long rather rough systolic bruit heard in the upper part of the left chest with maximum intensity in the second left interspace, with conservation, accentuation, or reduplication of the pulmonary second sound.
3. Gerhardt's ribbon dullness.
4. Radiological evidence of dilatation of the pulmonary artery.
5. Comparative absence of symptoms.

The association of any three of the above in a patient we consider to be sufficient for diagnosis. The presence of a machinery murmur is of itself sufficient for diagnosis.

Authors' series of cases.

The 20 cases outlined and analyzed below (see Appendix) have for the most part occurred either in school children or in hospital practice. In the examination of these cases our routine has been to measure height and weight, proceed to the clinical examination, and then subsequently examine them radiologically with a standard seven-foot technique. Certain of the patients, if not too young, have been investigated with the polygraph, and a few with the electrocardiograph.

Of the 20 cases in this series 7 are males and 13 are females. The youngest is 5 and the oldest 21.

As regards the mode of the initial discovery of a cardiac lesion, 15 of the patients learnt of its existence at the routine school examination, and 5 had the lesion discovered during the course of some infectious disease such as measles (2), pneumonia (1), or influenza (2). Three of the patients have known of the existence of their lesion for 9 years or longer.

Physical development.—As regards physical development the patients were compared with average tables of school children of corresponding age. Contrary to expectation 6 were of average development, 9 were definitely above the average, and only 5 were under average. The slender gracile build was conspicuously absent. One only appeared definitely anæmic.

Symptoms.—Fifteen of the cases were completely free of symptoms and devoid of all complaints at the time of examination. Two of the patients complained of pain round the heart, one a child aged 12, and the other a male aged 21. In the latter case the pain was substernal, radiated to the left shoulder, scapula, and down the inner side of the left arm. It was provoked by exertion and disappeared with rest. When the pain subsided a sensation of warmth supervened in the areas in which pain had been felt. There was no electrocardiographic abnormality. Another patient aged 12 complained of vague chest pains. In 2 cases a neurosis was present and this had been fostered by an incorrect diagnosis in the first instance and by parental anxiety and complete restriction of all physical activity. Tachycardia on slight exertion was present in 1 case. Signs of infective endocarditis were present in 1 case. Dyspnœa and palpitation on exertion were complained of in the 2 elder patients. Transient cyanosis occurred with infection in 3 cases. In 1 case, two fits in which the child had been blue, had preceded the discovery of the lesion by 2 years, and in yet another, fits had occurred in earliest infancy. If one fact emerges from the study of these cases it is the relative absence of symptoms.

Physical signs.—In no case was the heart greatly enlarged on clinical examination, nor was dullness detected to the right of the sternum. Gerhardt's ribbon dullness was found to be present in 7 patients, the youngest

being a female of 5 years of age. A systolic thrill was found in 12 cases, i.e., 60 per cent. In 1 case it was felt diffusely over the præcordia; in the others it was felt over the upper part of the left side of the chest with maximum intensity in the second left interspace close to the sternum. There appeared to be no correlation between the existence of a thrill and a machinery murmur. A thrill and a continuous murmur were present in 7 cases in the series and a systolic bruit with a thrill in 2 cases. A continuous or machinery bruit was found 12 times (60 per cent.) in the series. In 1 case it was maximum in the first left interspace, and in 11 in the second left interspace close to the sternum. In 6 of the cases the continuous element of the bruit was appreciable as low as the third left interspace and the fourth costal cartilage.

From our investigation it would appear that no definite statement can be made as to the age at which a machinery murmur can first be heard. It was heard in one case at the age of 5, and was accompanied by notable prominence of the middle arc in the frontal position. On the other hand a machinery murmur may be present at any early age without notable prominence of the pulmonary arc, such dilatation of the pulmonary artery as is present being detected only on examination in the oblique position. Further work is required amongst school children in order to discover the age at which the systolic bruit becomes continuous. The association of a systolic bruit and thrill in the second left space, with absence of cyanosis and with an accentuated pulmonary second sound, should always lead to suspicion that a patent ductus is present. In this connexion it may be recalled that occasionally a continuous murmur is best recognized when the subject is erect.

A diastolic murmur was heard in 3 cases along the left border of the sternum. In none of these cases was there any history of rheumatic infection. One case at autopsy was found to have recent vegetations on the aortic valve as part of an infective endocarditis[10]. In all cases the pulmonary second sound was well heard and in 4 of them it was reduplicated.

X-ray examination.—(See illustrations in appendix, pp. 299 and 301).—We have found the X-ray examination of considerable value in confirmation of the diagnosis of this condition. Perry[3] was of the opinion that X-ray examination was of little value in the elucidation of congenital cardiac pathology, and in particular quotes Lincoln and Spilman[9] as stating that the pulmonary arc of the left cardiac border was enlarged and prominent in as many as 21·3 per cent. of normal children. In Perry's own series of congenital heart cases the pulmonary arc was prominent in 26·8 per cent.

In 16 of our 20 cases the pulmonary arc was prominent in the frontal position and a machinery bruit was associated with 10 of these. A machinery bruit was present without notable prominence of the pulmonary arc in 1 case. In the remaining cases the diagnosis rested on purely clinical grounds.

In all cases careful search was made for notching of the under surfaces of the ribs significative of a coarctation of the aorta which was considered as a possible associated defect likely to escape notice.

Electrocardiogram.—An electrocardiogram taken in 5 cases was physiological. There was no abnormal axis deviation. In 3 cases the QRS complexes were tall in leads II and III and in 1 case low voltage was present in all 3 leads.

Differential diagnosis.—A patent ductus arteriosus has to be diagnosed from other congenital defects, from conditions in which a hæmic or functional murmur is present, and from rheumatic heart disease.

In the presence of a continuous murmur, localized in the second left space, there should be no difficulty as this bruit is pathognomonic. In those cases in which a harsh systolic bruit is maximum in the second left space with absence of cyanosis and clubbing, the presence of a well-heard or accentuated or reduplicated pulmonary second sound will serve to differentiate the condition from pulmonary stenosis, for in this latter condition the pulmonary second sound is weakened or absent, although an accentuated second sound has been recorded in pulmonary stenosis by Eakin[11].

In cases in which there is an inter-ventricular septal defect, the murmur is generally loudest in the third and fourth left spaces close to the sternum, and is heard with diminishing intensity towards the apex and left clavicle.

In general it may be said that the bruit in congenital heart disease is remarkably constant in localization and in character. Some of the children have been observed over years without any marked alteration in the clinical signs.

Hæmic bruits are as a rule blowing in character and are susceptible to change in the position of the subject, and vary with the phase of respiration.

Differentiation from rheumatic heart disease rarely presents any great difficulty. The bruits of rheumatic valvular disease have a different localization, and are associated with modifications in the cardiac sounds, and frequently with enlargement of the heart.

The history of the case is often of the utmost value in diagnosis. A history of rheumatic infection may be given. Of great importance in a difficult case is the history of the discovery of a cardiac lesion. If there has been knowledge of a cardiac lesion since early infancy or since below the age of 5, it is strong evidence in favour of a congenital abnormality, as the incidence of rheumatic heart disease is mainly after 5 years of age.

Contrary to the opinion expressed by Perry[3] we have found the X-rays of considerable value in diagnosis. The radiological features of a patent ductus arteriosus are sufficiently definite to be of value in the differentiation from other congenital conditions. Evidence may not always be striking in very young children but it is frequently so in older subjects. It is particularly useful in the confirmation of such a sign as Gerhardt's dullness. Other heart conditions in children, such as pulmonary stenosis, and particularly the tetralogy of Fallot, have rather characteristic pictures which are helpful in differential diagnosis. Mitral stenosis can be readily recognized in the oblique position with barium in the œsophagus.

Conclusions.

1. Twenty cases are presented in which clinical and radiological examination have suggested a diagnosis of a patent ductus arteriosus.

2. Certain criteria necessary to establish a diagnosis have been suggested. A combination of any three of the following signs are considered as adequate for a diagnosis.

   a. The presence of a continuous or machinery bruit in the second left space.

   b. The presence of a long rough systolic bruit with maximum intensity in the second left interspace, with conservation, accentuation, or reduplication of the pulmonary second sound.

   c. Gerhardt's ribbon dullness.

   d. Radiological evidence of dilatation of the trunk of the pulmonary artery.

   e. Comparative absence of symptoms.

3. No direct relationship can be established between the presence of a machinery murmur and thrill, or between any degree of dilatation of the pulmonary artery and a machinery bruit.

4. In cases that exhibit Gerhardt's dullness, radiological confirmation is always forthcoming.

5. Radiographic examination has a definite value in the differentiation of this condition from some other forms of heart disease in children.

6. Investigation is still necessary to establish the average age and the conditions under which a continuous murmur may appear. This can probably be best accomplished in a heart clinic maintained in connexion with a well organized school medical service.

Our thanks are due to Drs. Morrison and Watt of the Hull School Medical Service, and to Dr. Southey of the Grimsby School Medical Service, for valuable help given in segregating these children at school medical examinations; and to Dr. Bannen and Mr. S. Dolby for the radiograms.

(For References see page 302.)

APPENDIX.

Summary of cases.

Case 1 (Fig. 1).—Female, aged 11, presents no symptoms. Lesion has been known of for seven years. Undersized. Machinery bruit heard in the second left space. Systolic thrill in the left infraclavicular region. Systolic bruit audible along the left border of the sternum and at the apex. Pulmonary second sound well heard. X-ray evidence positive.

Case 2 (Fig. 2).—Female, aged 9. No symptoms, and lesion known of for four years since its detection at the routine school examination. Machinery bruit in the first left space. Systolic bruit heard at the apex, and a diastolic bruit along the left margin of the sternum. Pulmonary second sound well heard. Systolic thrill in the second left space and Gerhardt's dullness present. She is above the average in development and there is no history of rheumatic infection or indeed of any illness. X-ray evidence positive.

Case 3.—Female, aged 19. Has had knowledge of her lesion for nine years and has never done any physical exercise. Well marked neurosis present. Complains of pains round the heart, dyspnœa, and palpitation on exertion. Of average development, she is said to have had anæmia in the past. Machinery murmur in the second left space with systolic thrill in the same situation. Pulmonary second sound reduplicated. Gerhardt's dullness present. Electrocardiogram shews low voltage in all three leads. Polygraph shews inequality of the pulses, the right being greater than the left. X-ray examination positive.

Case 4 (Fig. 3).—Male, aged 21. Of average development. Has known that he has had a cardiac abnormality for 11 years. Complains of pains round the heart on exertion. The pain is substernal, passes to the left scapula and to the left shoulder, from whence it passes down the inner side of the left arm. It is relieved by rest, and as the pain passes away a sensation of warmth comes to the regions where the pain has been felt. Machinery murmur in the second left space. Diffuse systolic thrill. Diastolic bruit present along the left sternal margin. Pulmonary second sound reduplicated. No cardiac enlargement detected. Inequality of the pulses shewn with the polygraph. Electrocardiogram physiological. X-ray examination shews dilatation of the pulmonary artery most marked in the oblique view, the frontal view shewing little more than fullness of the arc. Patient despite his handicap and a certain element of neurosis is in active work as a labourer. There is no history of rheumatism.

Case 5.—Male, aged 6. Lesion which was hitherto unsuspected, detected at the routine school examination at the age of 5. Above the average in development, and no symptoms present. A long harsh systolic bruit is present and maximum in the second left space. Pulmonary second sound accentuated. X-ray shews prominence of the pulmonary arc. Patient has in addition facial asymmetry and epicanthic folds.

Case 6.—Female, aged 10. Of average development and no symptoms. Lesion first discovered at the routine school examination. Machinery bruit and systolic thrill in the second left interspace. Pulmonary second sound well heard. X-ray evidence positive.

Case 7 (Fig. 4).—Female, aged 12. Average size and no complaints. Lesion found at recent school examination and was apparently not detected at the school entrance examination. Machinery murmur present in the second left space without accompanying thrill. Pulmonary second sound accentuated and Gerhardt's dullness present. X-ray examination positive.

Case 8.—Female, aged 12. Rather undersized, and complains of precordial pain under any circumstances. Systolic bruit maximum in the second left space, and heard faintly at the apex. Pulmonary second sound accentuated. Pain has only been complained of since the detection of the lesion, two years ago, in an apparently healthy child at the routine school examination. Radiological examination typical picture of patent ductus.

Case 9.—Female, aged 6, of average size and no symptoms. Lesion was found at the routine school examination. Systolic bruit maximum in the second left

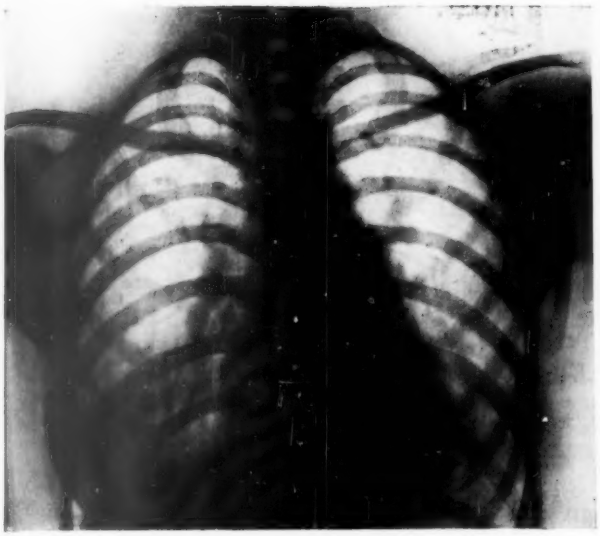

FIG. 1.—Case 1.

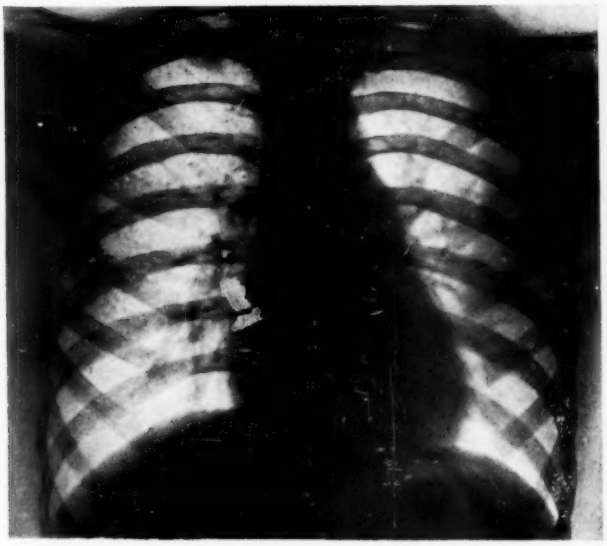

FIG. 2.—Case 2.

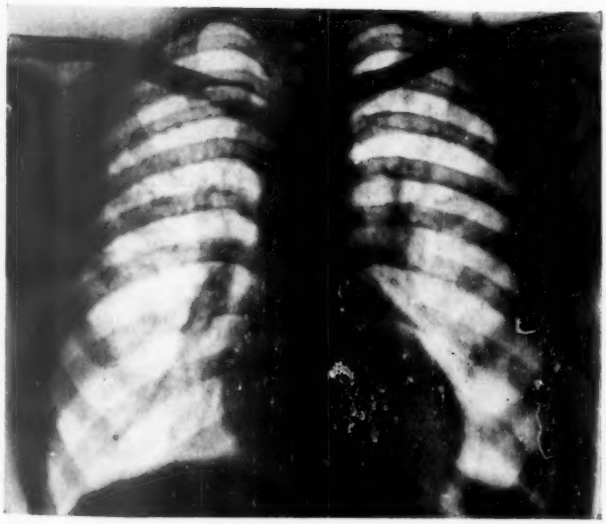

FIG. 3.—Case 4.

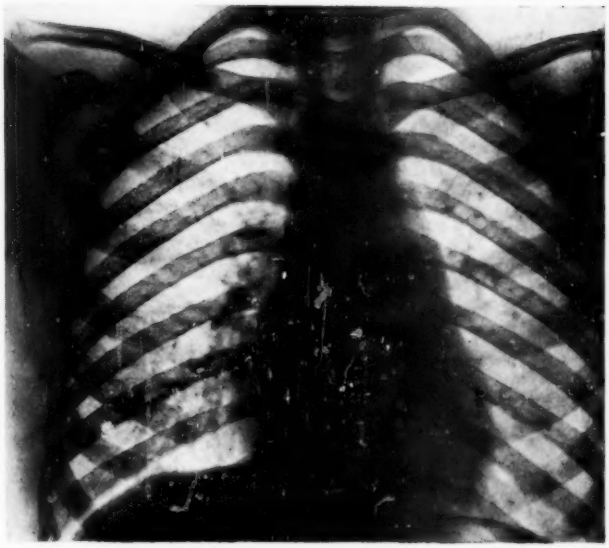

FIG. 4.—Case 7.

interspace, with accompanying systolic thrill. Pulmonary second sound well heard. Gerhardt's dullness present. X-ray shews prominent pulmonary arc.

Case 10.—Male, aged 12, of average size and no symptoms. Machinery murmur with accompanying systolic thrill in the second left space. Systolic bruit was audible at the apex. Pulmonary second sound accentuated. The lesion has been known of since measles four years ago. X-ray examination positive. Subsequently he developed an infective endocarditis with involvement of the aortic valves and the ductus. This case is recorded in more detail elsewhere[10].

Case 11 (Fig. 5).—Male, aged 16. Above the average in size, and leading an active life with no symptoms. Lesion discovered on leaving school. No cardiac enlargement. Systolic murmur and thrill in the second left space. Pulmonary second sound accentuated, and Gerhardt's dullness present. X-ray shews a prominent left middle arc.

Case 12.—Male, aged 6. Above the average in size, and no symptoms. Lesion detected at the age of three during an intercurrent infection. Systolic bruit maximum in the third left space with systolic thrill best felt in the second left space. Diastolic bruit along the left sternal margin, and pulmonary second sound well heard. X-ray examination positive.

Case 13 (Fig. 6).—Male, aged 15, with no complaints, and knowledge of the existence of the lesion since the school examination ten years ago. Systolic bruit and thrill maximum in the second left space. Pulmonary second sound well heard. Above average in development, leading an active life. X-ray examination positive.

Case 14.—Female, aged 9. Below average size but with no symptoms. Lesion found at the school entrance examination four years ago. Machinery murmur present in the second left interspace, but no thrill. Pulmonary second sound accentuated. X-ray evidence positive.

Case 15.—Female, aged 12. Above the average in size, but with no symptoms, and with knowledge of a cardiac abnormality for two years. Machinery murmur in the second left space with no thrill, and an accentuated pulmonary second sound. X-ray examination positive.

Case 16.—Female, aged 7. No symptoms and above the average in development. The lesion was found recently at the school medical examination. Machinery murmur in the second left space with no thrill. Pulmonary second sound well heard. X-ray evidence positive.

Case 17 (Fig. 7).—Female, aged 13. Under average in size. The lesion was only recently found. Systolic bruit maximum in the third left space with a well heard pulmonary second sound. X-ray examination positive.

Case 18 (Fig. 8).—Female, aged 13, with no symptoms and above the average in development. She has known of the lesion for a year since it was found at the school examination. Systolic bruit and thrill in the second left interspace, with reduplication of the pulmonary second sound. Gerhardt's dullness present. X-ray evidence positive. Electrocardiogram physiological.

Case 19.—Female, aged 5. Rather small and thin and slightly below average. Heart lesion found at the routine school examination. No symptoms are present. She had two fits about two years ago in which she became blue. These were, however, not attributed to her heart. Machinery murmur in the second left space with accompanying systolic thrill. Gerhardt's dullness present. Pulmonary second sound reduplicated. X-ray examination positive.

Case 20.—Male, aged 12. Complains of vague pain in chest and some shortness of breath on exertion. His lesion was discovered when he had pneumonia at the age of 4. His brother apparently died of a congenital heart lesion with superadded infective endocarditis. No thrill present. A continuous murmur was best heard in the second left space with the subject erect. The systolic murmur was heard at the apex, in the left carotid, and very well in the left interscapular region behind. Pulsation poorly felt in the femoral vessels. He is above the average in development. X-ray examination shews rounded prominence of pulmonary arc,

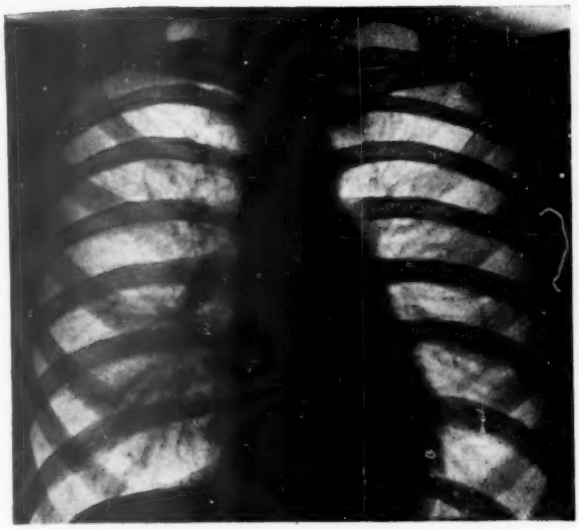

FIG. 5.—Case 11.

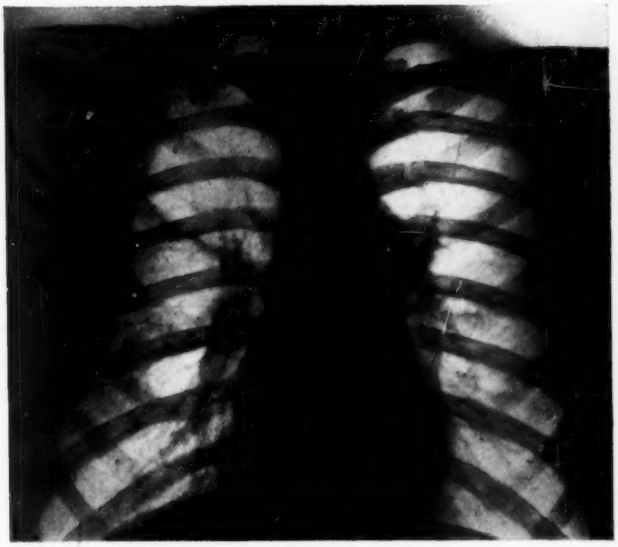

FIG. 6.—Case 13.

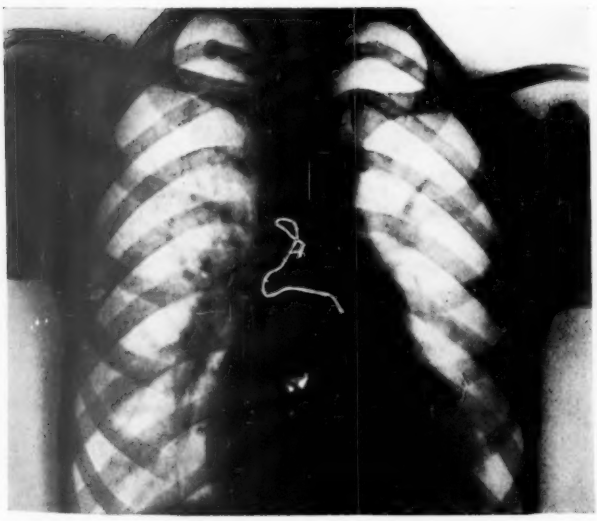

FIG. 7.—Case 17.

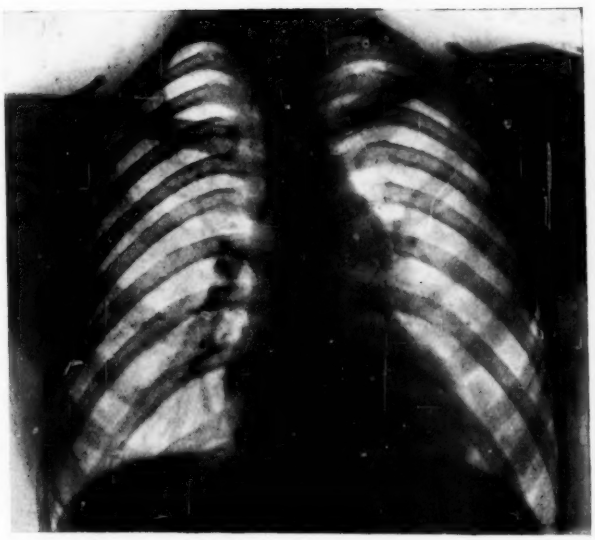

FIG. 8.—Case 18.

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OBESITY AFTER CHOREA

BY

ALAN MONCRIEFF, M.D., M.R.C.P.

(From the Hospital for Sick Children, Great Ormond Street, London.)

The occurrence of obesity after various infectious diseases, such as typhoid fever, for example, has been noted by many observers[1]. In most instances this is attributed to lack of exercise, dietetic changes, or endocrine disorders consecutive to the acute disease and the convalescent period. When, however, obesity begins to develop abruptly after an acute disease involving the central nervous system, the question arises whether it is caused by inflammatory changes in the region of the pituitary body and adjacent parts of the brain. In connexion with chorea the occurrence of obesity has therefore the special interest that it may possibly give some indication of the extent of lesions in the brain in that condition. Two children recently attending the out-patient department at the Hospital for Sick Children, Great Ormond Street, exhibited extreme degrees of adiposity which dated from an attack of chorea, and this led to a search of the records for further cases and a survey of the scanty literature on the subject.

Clinical records.

Case 1.—Girl, aged 8 years, 4 months. This patient had her first attack of chorea at the end of 1930 and shortly afterwards began to get fat. Her father and mother are not abnormally fat and there are two other children in the family, both of normal build. When she came under observation this patient weighed 87½ lb. the normal weight for her age being 54½ lb. In all other ways she was a normal child, the heart being unaffected. The excessive adipose tissue was distributed in the usual feminine sites. There was no mental retardation and she was quite active. X-ray examination of the pituitary fossa showed no abnormality as regards size or shape. A sugar tolerance examination showed a slight delay in return to normal levels of the blood sugar, but such a small degree of diminished sugar tolerance is probably of no significance. The figures were as follows:—

Blood sugar, fasting	...	...	119	mgrm.	per	100	c.cm.
,, ,, after ½ hour	...	160	,,	,,	,,	,,
,, ,, ,, 1 ,,	...	128	,,	,,	,,	,,
,, ,, ,, 1½ hours	...	110	,,	,,	,,	,,
,, ,, ,, 2 ,,	...	84	,,	,,	,,	,,
,, ,, ,, 3 ,,	...	105	,,	,,	,,	,,

Thirty-five grm. of dextrose were given. No glycosuria occurred during the test.

Case 2.—Girl, aged 10 years, 8 months. This child was admitted to hospital in October, 1930, with her third attack of acute chorea in two years, and was then transferred to a special rheumatism convalescent home. On discharge at the age of 10 years in November, 1931, she weighed 65½ lb., the normal for age being 64 lb. Examined at that time she presented the appearance of a normal child, the heart

being unaffected. She returned to an ordinary school and led an ordinary life. During the next few months she began to put on weight at a great rate. By July, 1932, she weighed 89 lb. a gain of nearly 24 lb. in eight months. X-ray examination of the pituitary fossa showed no abnormality and a sugar tolerance examination was normal. The figures were:—

Blood sugar, fasting	...	...	119	mgrm.	per	100	c.cm.
,, ,, after ½ hour	...	160	,,	,,	,,	,,
,, ,, ,, 1 ,,	...	128	,,	,,	,,	,,
,, ,, ,, 1½ hours	...	110	,,	,,	,,	,,
,, ,, ,, 2 ,,	...	84	,,	,,	,,	,,
,, ,, ,, 3 ,,	...	105	,,	,,	,,	,,

Thirty-five grm. of dextrose were given. No glycosuria occurred during the test.

Discussion.

These two patients received nothing out of the ordinary in the way of treatment, which was the same as regards rest and convalescence as other cases attending the hospital. To serve as a comparison all children who had had chorea, attending the same out-patient clinic, were investigated as regards their weight before and after the acute illness. There were 20 such children in all, and every one had suffered from chorea, with or without cardiac involvement, during the past few years. Of the 20 children, 7 have remained within 10 per cent. of the normal weight for age, 7 are 10 per cent. or more below, and 6 are 10 per cent. or more above the normal weight for age. Of the total 20 cases 6 are boys and 14 are girls, while of the 6 over-weight cases 5 are girls and 1 is a boy. Analyzing these 6 cases in more detail it is found that the boy and 3 girls were definitely over-weight before the attack of chorea, and the remaining 2 girls were normal in weight before the attack. These are the 2 patients who form the subject of these comments. The other 4 over-weight children are none of them abnormally fat, and the increase since chorea has not been excessive.

It seems fair to attribute to the chorea some part of the ætiology of the adiposity in such cases. Dunlop and Murray Lyon[2] in a recent study of obesity mention its occurrence after rheumatic endocarditis and attribute it to lack of exercise. But it is significant that, especially in Case 2, the adiposity did not develop during prolonged rest in a convalescent home, but only when, the disease process being over, the child returned to ordinary life. Neither of the girls is near enough to puberty to explain the increase in weight by the well-recognized tendency to adiposity occurring at this period of development.

Previous records.—Published cases of this condition are scarce in number. The most important contribution to the subject is by Coburn[3] who mentions obesity following chorea in seven instances out of his great study of 3,000 rheumatic subjects. He defines the condition as one in which a child previously of normal proportions becomes obese shortly after the characteristic manifestations of Sydenham's chorea have subsided. One

patient described by Coburn went from a normal of 88 lb. to 166 lb. during the few months after recovery from chorea. He states that ' this striking development of adiposity is perhaps an objective indication of cerebral changes, possibly in the region of the hypophysis.' Another important paper is by Gamna[4] who describes a case of the ' syndroma adiposo-genital ' following rheumatic chorea. This was in a boy of 12 who had excessive adipose tissue distributed in the feminine situations. The pituitary fossa was normal. Gamna suggests a lesion in the region of the tuber cinereum or hypothalamus.

Adiposity has been described after other acute affections of the central nervous system, and this has also some bearing on the type and site of the lesion in chorea. After epidemic (lethargic) encephalitis the development of adiposity is well recognized. Hall[5] in his work on this disease describes a large literature on the subject, and von Economo[6] also refers to ' traces of dystrophia adiposo-genitalis ' in children following encephalitis lethargica. Raab[7] has described an interesting example of abnormal adiposity following post-vaccinal encephalitis and Babbonneix, Robin and Lebourdy[8] showed before a medical society in Paris a girl of 15 with obesity, amenorrhœa, alopecia and choreiform movements which were all attributed, on slight evidence, to congenital syphilis. A valuable paper on obesity in childhood by Nobécourt[9] contains reference to a group of ' obésités d'origine encephalique,' and he attributes these to lesions in the floor of the third ventricle in the region of the tuber cinereum. He states that such obesity may occur after cerebral tumour, hydrocephalus, encephalopathy, epidemic encephalitis and perhaps following polioencephalitis, chronic meningitis and cerebral trauma.

Prognosis and treatment.—It is not possible from the existing literature to come to any definite conclusions about prognosis, and the two cases here described will be carefully observed on this point. As regards treatment this is being carried out on general principles. The children are being given a diet with limited carbohydrates and fats, and exercise is encouraged. Both are receiving small doses of thyroid gland which is being gradually increased, and one is having as well whole-gland pituitary.

I am indebted to Dr. B. E. Schlesinger for permission to publish these cases and for his interest in the subject. Dr. B. Shires kindly took the skiagrams and Dr. W. W. Payne carried out the biochemical investigations.

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OTITIS MEDIA AS AN ÆTIOLOGICAL FACTOR IN GASTRO-ENTERITIS*

BY

LEONARD FINDLAY, M.D., D.Sc., M.R.C.P.,

Physician, East London Hospital for Children.

The idea that otitis media is a possible factor in the ætiology of acute gastro-enteritis is by no means of recent date. Ever since the sixties of last century this is a view which has been stressed periodically, and, although not generally accepted, it has received support particularly of otologists and morbid anatomists.

One of the most remarkable features in the pathology of children's diseases is the absence of any naked-eye or microscopic lesion in the alimentary tract of children dying of severe gastro-enteritis. It is the case of pneumonia, pyelo-nephritis or marasmus with a terminal or passing diarrhœa which presents an abnormality of the gut. Frequently, however, although in my opinion not so often as is generally stated, pus is found in one or both ears. Occasionally a suppurative nephritis may be detected but the most common post-mortem finding is broncho-pneumonia. From the localization and histological characters it is possible to express an opinion regarding the age and type of the pneumonia, but unfortunately this is not so in the case of otitis. So far as I am aware, one cannot decide from the morbid anatomy the duration of the inflammation of the middle ear, and thus whether it was, or was not, in existence prior to the onset of the gastro-enteric symptoms. This of course is the crux of the matter. No doubt the adherents of the hypothesis that otitis media is the cause of gastro-enteritis are influenced by the doctrine of focal sepsis, which has been a favourite explanation of any disease of still undecided ætiology, as pernicious anæmia and rheumatoid arthritis amply testify.

In contrast to otologists and morbid anatomists, pædiatricians for the most part have been sceptical that in focal sepsis, of which otitis media is only one example, is to be found a serious cause of gastro-enteritis, and for this scepticism there are several good reasons. In the first place, it must be remembered that of all the functions during infancy nutrition is the most important. At no other period of life is growth so rapid. Digestion and

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* Based on remarks made at discussion on Otitis Media in Infancy by Laryngological Section of British Medical Association, 27th July, 1932.

absorption are working, as it were, at concert pitch and in consequence are easily upset. But whatever the explanation, there is no doubt that in the symptomatology of disease during infancy the most constant features are those of interference with nutrition and gastro-intestinal disturbance. Those of us who have the care of infants appreciate that illness during this age-period is more frequently reflected in the weight curve than in that of the temperature. We also know that whether the illness be one of the gastro-intestinal tract, or one of some organ far removed, vomiting is the most common early symptom. Vomiting in infancy takes the place of a shivering or rigor in the adult. And further, instead of constipation, which is the rule in any febrile illness in the adult, diarrhœa, or at least a looseness of the motions, is in similar circumstances not unusual. To this rule acute otitis media is no exception.

It is because of this peculiarity of infancy that it is unfortunately a common error to diagnose in the very young all sorts of conditions, e.g., broncho-pneumonia, pyelo-nephritis, poliomyelitis, meningitis, etc., as gastro-enteric in nature. Indeed, this fact has taught pædiatricians never to make a diagnosis of gastro-intestinal mischief until a complete physical examination (not omitting the ears) has failed to reveal any other cause of the symptoms. It may be remarked, however, that although the gastro-intestinal symptoms may dominate the clinical picture, when these are secondary to some non-alimentary disease, they are never of the severity of true gastro-enteritis, nor are they usually accompanied by the coma, dehydration and Hippocratic facies so characteristic of that condition.

In this connexion it is interesting to contrast the incidence and nature of the gastro-intestinal symptoms in those examples of pneumococcal meningitis in which disease of the ear is probably the ætiological factor, with those in which otitis plays no part, i.e., cases with and cases without otitis media. Of 18 cases of pneumococcal meningitis with otitis media in children under one year of age, seven suffered from severe vomiting, and diarrhœa was a marked feature in five of the children. In only one case, however, was there any dehydration and an appearance such as is characteristic of true gastro-enteritis. This child had been ill for one month and presented, in addition, pyuria and broncho-pneumonia. On the other hand, of 18 infants suffering from pneumococcal meningitis without otitis media, as verified at post-mortem examination, severe vomiting was present in eight of the cases and diarrhœa in five, i.e., in practically the same proportion.

Comparison of gastro-enteritis and otitis media

Social incidence.—As previously mentioned the cause of gastro-enteritis is still uncertain. It may be that there are several causes but, whatever the nature of the ætiological factor, there are certain features in the life history of the disease which make it unlikely that otitis media plays an important rôle in this direction. One of the most striking is that gastro-enteritis is a disease which is almost entirely limited to the hospital classes. Although one

constantly meets it in the out-patient departments and wards of the hospital, I have only records of having seen in private practice 12 cases during the 10 years 1920 to 1929 inclusive. On the other hand, during this same period, I have seen in private practice 32 infants with uncomplicated otitis media.

Past feeding.—Equally striking with the social incidence of gastro-enteritis is its almost exclusive occurrence in the bottle-fed child. Of 320 infants admitted to hospital with gastro-enteritis during the course of six years, in whom I have definite information regarding the nature of the feeding at the time of the onset of the illness, only 9 per cent. were breast-fed. I have no comparable figures in connexion with uncomplicated otitis media, although I should be astonished to learn that it would present the same predilection for the bottle-fed child. I have, however, details regarding the nature of the feeding in 18 hospital infants admitted with pneumococcal meningitis and pneumococcal otitis media, and of these 44 per cent. were breast-fed. If it is permissible to take this incidence of otitis media as a measure of that prevailing in the breast-fed child generally, then it would appear that, if this septic focus has anything to do with gastro-enteritis, it is practically only in the bottle-fed child that it exerts its pernicious effect, a conclusion which is most assuredly untenable.

Seasonal incidence.—Another characteristic feature of gastro-enteritis is its special prevalence during the warmer months of the year, e.g., July, August and September, and especially is this the case when the disease assumes epidemic proportions. For example in 1921, when there occurred the last real epidemic in the west of Scotland, and for that matter in Britain, 64 per cent. of the cases admitted to the Royal Hospital for Sick Children, Glasgow, came under observation during that trimester; whereas in the year 1928, when the disease was not unusually prevalent, only 44 per cent. of the examples occurred during this period of the year. One would expect, on the other hand, that otitis media would be most prevalent during the colder months of the year and this at least has been my experience. I have no records of the seasonal incidence of otitis media in hospital cases but I have details regarding the examples seen in private practice and these show that only 12·5 per cent. occurred during these three months, while 50 per cent. occurred during the winter and spring. It may also be mentioned that of the examples of pneumococcal meningitis with otitis only 20 per cent. came under observation during the months of July, August, and September. It may be argued, of course, that I am referring to a type of gastro-enteritis which is a specific infection, and a disease sui generis and not the variety caused by otitis media. To this I reply that it was during the epidemic in the summer of 1921 that Renaud[1] in Paris studied the disease, formulated his conclusions regarding the rôle of otitis media, and suggested mastoidectomy as the proper line of treatment.

Myringotomy in gastro-enteritis.—My introduction to this question was by that master clinician Finkelstein[5], who was very emphatic that otitis media was not the cause of gastro-enteritis and advised against interfering

with the ear unless local symptoms demanded it. This was my own practice for many years. However, in view of the continued ignorance of the true cause of this disease, and the reports from France[1] and America[2, 3] of good results from attacking the ear, I was tempted some years ago to test this line of treatment for myself. At first I contented myself by incising the drum in all cases in which pus was suspected. The results were quite inconclusive. Seldom did we see any immediate response, especially when enteritis was a marked feature, and the course of the disease did not appear to be materially affected. Indeed, at times we got the impression that we had done harm by our interference. Quite otherwise was it when myringotomy was performed in a case uncomplicated by gastro-enteritis. But in order to make a better test it was decided that in one ward all ears should be treated while in another ward the ears should be left alone. Still we could not see any definite effect in response to this line of therapy.

Mastoidectomy in gastro-enteritis.—If, however, as is frequently stated, the inflammation in the middle ear invariably extends to the mastoid antrum no great benefit can be expected from simple myringotomy, since by this operation only a part of the focus is attacked. But this extension of the disease to the mastoid antrum is in the vast majority of cases pure assumption. In my experience pus in the middle ear does not necessarily mean pus in the antrum. This is a point of considerable importance in our evaluation of the otitic hypothesis of the cause and of the therapy of gastro-enteritis recommended by certain French and American schools. In a consecutive series of 15 post-mortem examinations on infants with otitis media under my own care, pus was present in one or both antra only in four, i.e., 26 per cent.

Since, however, it is impossible on clinical grounds to eliminate extension to the mastoid antrum, and being influenced by the teachings of the French and Americans, I had, during the autumn of 1928, nine cases submitted to double antrotomy. Seven died and two recovered. A review of the cases shows that the two which recovered were not seriously ill. In neither was there any great depletion, nor was the weight falling, so that it is possible that they would have recovered had they been left alone. I suggest this because the most valuable prognostic features in gastro-enteritis are the apparent severity of the illness and the degree of dehydration which the child presents on coming under observation. For example, of 43 children noted as being very ill on admission to hospital 50 per cent. died, whereas of 38 described as not very ill only 5 per cent. succumbed.

In the case of the seven children who died five were considered on admission as not very ill. Nor was the operation of mastoidectomy performed as a last resort. In two instances both antra were opened within 24 hours of admission to hospital and in another case within four days. It is also interesting to record that in one of the cases which came to post-mortem examination, the pathologist stated that the pus was confined to the middle ear and that the antra presented no sign of inflammation, although the

surgeon was convinced that pus was evacuated at the time of the mastoidectomy. No one, I feel sure, could consider these results encouraging; at any rate they induced me to abandon this line of treatment.

A study of the French and American literature dealing with this line of therapy, on which be it remembered the hypothesis of ætiology is based, can, I feel sure, also engender nothing but scepticism. Renaud in 1921, which was as I have already mentioned an epidemic year, claimed that otitis media was the cause of gastro-enteritis and reported that he performed paracentesis in 36 cases with a recovery rate of 38 per cent. and in 10 mastoidectomy with a recovery rate of only 10 per cent. It was in 1925 that the Americans[2] first stated that myringotomy favourably influenced this disease. In 1927, however, we find the same authors[3] recommending that, if the results which they had previously claimed for myringotomy were to be got, mastoidectomy must be performed. Still later they assert that if mastoidectomy is to be successful the operation must be performed under a local and not a general anæsthetic. But surely the climax was reached in 1928 when we find Odeneal[4] writing that, if the child does not improve with mastoidectomy, the nasal accessory sinuses, which he states are infected in 50 per cent. of cases, should be opened and drained.

Causes of nutritional disease in infancy.

Nutritional disease in infancy can be divided into two main groups—the toxic and the non-toxic. In both there is failure to gain in weight, or actual loss of weight, but in the one group (gastro-enteritis or intoxication) there is evidence of gastro-intestinal irritation (diarrhœa) and toxic symptoms, whereas in the other (marasmus or athrepsia) these toxic and irritative manifestations are conspicuous by their absence. It is important to bear in mind that the one type may lead to and pass into the other, and that both varieties render the child susceptible to all sorts of septic and microbic infections. In this way the clinical picture of nutritional disease becomes most complex, and the discrimination between cause and effect one of the most difficult problems in clinical medicine. We have learned that a large proportion of the non-toxic cases result from underfeeding, although chronic disease of various kinds may interfere with nutrition and reproduce an identical picture. The cause of the toxic variety is, however, still undecided. It certainly has not been demonstrated that focal sepsis, and especially otitis media, is a serious responsible factor. Otitis media, just as pyelonephritis and broncho-pneumonia, frequently develops during the course of the nutritional diseases and no doubt increases the gravity of the case, but our chief aim is to cure the primary condition which is rendering the child less resistant. It must also be appreciated that a child the subject of otitis media, and especially if being artificially fed, may contract gastro-enteritis. It may even be assumed that in consequence of the otitis the child has been rendered more liable to gastro-enteritis. Nevertheless, the gastro-enteric infection is the major problem and demands first consideration.

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OSSEOUS DYSTROPHY FOLLOWING ICTERUS GRAVIS NEONATORUM

BY

FRANCES BRAID, M.D., M.R.C.P.,
Physican, Children's Hospital; Assistant Physician, Maternity Hospital, Birmingham.

It seems desirable to put on record the fact that two very unusual conditions, icterus gravis and osseous dystrophy, have occurred in one and the same child. That the two conditions have some interdependence is at least an interesting speculation.

Case report.

R. T., male, born on 5th November, 1928, was the second child of healthy parents. At birth he weighed 7 lb. 10 oz. His mother was well throughout the pregnancy, and her first child had always been healthy. About the second day he became jaundiced, but his condition did not arouse anxiety until the tenth day when he bled profusely from the mouth and umbilicus, and on that account he was admitted to the Nursery of the Birmingham Maternity Hospital. When first seen, he looked extremely ill, was deeply jaundiced and bleeding freely. A single dose (5 c.cm.) of whole blood, given intra-muscularly, caused prompt arrest of the bleeding; but, for the next three weeks, his condition remained critical. The jaundice was apparently stationary and the stools were consistently colourless. Repeated chemical tests for bile salts and bile pigment in the stools were negative. The liver and the spleen were not appreciably enlarged. His weight fell to 5 lb. 9 oz. at four weeks. Then a gradual improvement set in, and the stools began to assume a normal colour. On 8th December bile pigment was present in the fæces, but bile salts were still absent. He was entirely breast-fed and at the age of seven weeks he was able to go home. The yellow staining of his skin persisted for many weeks so that an extensive brown birth-mark on his face and neck was not noted until he was between four and five months old; but his general progress was good. At six months he had two teeth, and at eleven months he had seven teeth and was 15½ lb. in weight.

During this period, the fat content of the stools had been estimated on three occasions (Table 1).

TABLE 1.

ESTIMATION OF FAT IN FÆCES AT 2, 6, AND 9 MONTHS.

Date	Total fat in dried fæces	Percentage of fæcal fat		
		Neutral fat	Fatty acid	Soap
Jan. 5, 1929	66·5%	17·9	25·7	56·4
May 28, 1929	30·2%	44·8	29·4	25·8
Aug. 13, 1929	25·3%	6·7	47·4	45·9

About a year later, in response to my enquiry concerning his progress, his mother brought him to see me. He appeared to be very well apart from a certain degree of secondary anæmia:—red cells 3,755,000, hæmoglobin 58 per cent.; white cells 7,550; platelets 274,800; and reticulocytes ·3 per cent. He was bright and active in his movements, his mental development was up to normal standard and there was no lesion of his central nervous system. The only complaint was that he was unsteady on his feet. The reason for that became apparent a few months later when persistent pain in one thigh, after a fall, led to an X-ray examination being made and so to the discovery of a cystic condition of the shafts of all the long bones. On that account, he was admitted to the hospital, early in 1931, and submitted to various investigations.

Calcium and phosphorus metabolism.—The child was fed on Almata and milk, a complete food, for a week and on the second three days estimations were made. The results showed that calcium and phosphorus metabolism was within normal limits (Table 2).

TABLE 2.

CALCIUM AND PHOSPHORUS ESTIMATIONS. APRIL 18-20, 1931.

	Daily average (grm.)				Absorbed grm.	Retained grm.
	Intake	Fæcal output	Urinary output	Total output		
Calcium	1·1788	·373	·011	·384	·8058 (68·3%)	·7948 (67·4%)
Phosphorus	·9641	·1406	·3340	·4746	·8235 (85·4%)	·4895 (50·8%)

Fat excretion.—Fat excretion as estimated in the stools of three successive days was within normal limits. The slightly high total daily fat excretion in the third analysis was most probably due to the fact that the baby had recently had an operation for acute mastoiditis and was not wholly convalescent (Table 3).

TABLE 3.

ESTIMATION OF FÆCAL FAT: AVERAGE OF THREE DAYS.

Date	Diet	Total fat in dried fæces	Percentage of fæcal fat			Excretion per day grm.
			Neutral fat	Fatty acid	Soap	
April 22.31	Almata & milk	39·1%	31·5	9·7	58·8	1·8
May 17.31	Ordinary diet	29·1%	11·7	40·6	47·8	1·2
April 12.32	Ordinary diet	25·2%	12·7	29·4	58·0	2·4

Bones.—X-ray examinations have been made from time to time and the cystic condition of the shafts of all the long bones has remained fairly constant. The epiphyses do not appear to be involved (Fig. 1).

While kept at rest, deformity of the limbs has remained slight but since he has been allowed to sit up, he has developed a kyphosis and a certain degree of forward curvature of the sternum (Fig. 2).

Eruption of the teeth and the condition of the teeth have been normal.

FIG. 1.—Skiagrams showing cystic condition of bones.

Other investigations.—Examination of the urine was negative, and the blood urea as estimated on 8th March, 1932, was 23·5 mgrm. per cent. The Wassermann reactions of the child and of his mother were negative.

Course.—He has passed through a severe attack of measles, an attack of chickenpox and an acute mastoiditis for which a radical operation was necessary, all without any untoward happening. His general health is good and, mentally, he

is very alert (Fig. 2). The condition of his bones has altered very little and there has been no definite deterioration other than a slight increase in rarefaction, such as might be accounted for by these acute illnesses. If the blood phosphatase, as estimated by the method described by Kay[1], may be taken as a guide then an improvement is suggested by its fall from ·86 in June, 1931, to ·32 in April, 1932. It seems probable that there may be an ultimate spontaneous cure when growth has ceased.

Various treatments have been tried in turn: ultra-violet light, radiostoleum, thymus extract and raw thymus, and various liver preparations. Throughout, a

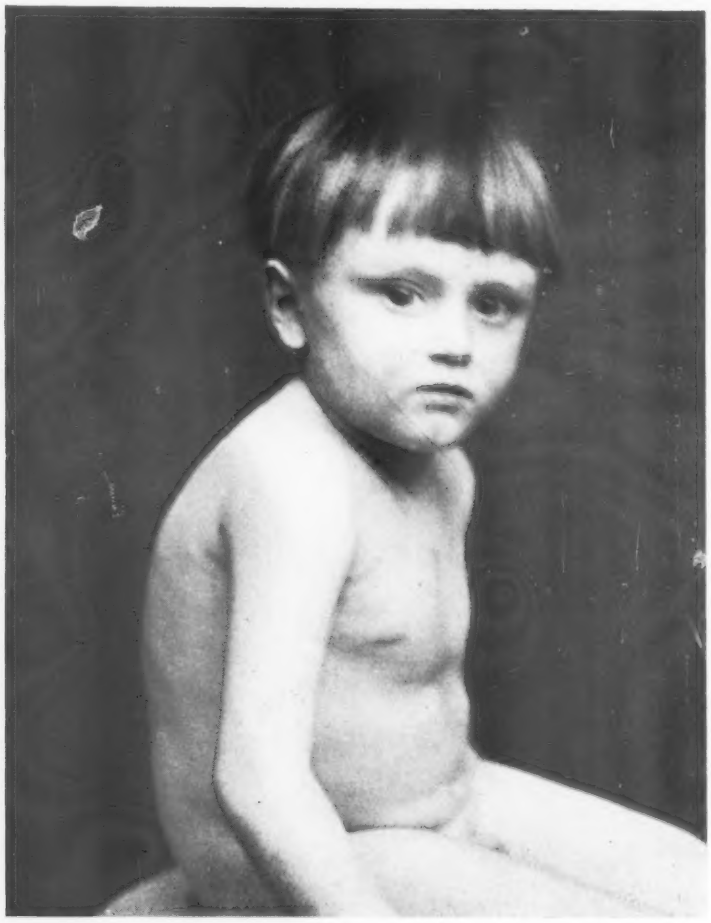

FIG. 2.—Showing kyphosis and curvature of sternum.

suitable diet and additional salts were given. No treatment has had any effect and the chief practical consideration has been the prevention of deformity.

Discussion.

Into which category should one place the jaundice of the early weeks of life in this case? My original diagnosis was congenital obliteration of the bile-ducts, but the subsequent progress of the case dismissed that possibility. It is interesting to note here, however, that, in his classical paper on

congenital obliteration of the bile-ducts, Thomson[2] included seven cases in which, at autopsy, the ducts were found to be pervious. Two of these had passed white stools, and in five there had been hæmorrhage from the umbilicus. The average life of these cases was seventeen and a half days, in contrast to an average of two and a half months in those in which the bile-ducts had been found to be impervious. It is very probable that these cases and the one here reported are similar, and fall into the group of familial icterus gravis. In the present case that diagnosis is supported by the fact that in January, 1931, another brother was born, who was deeply jaundiced, who bled and who recovered completely on treatment with repeated injections of whole blood.

The dramatic improvement in cases of familial icterus gravis neonatorum when treated with maternal serum or whole blood as recommended by Hampson[3], and the good immediate results, intensify the disappointment experienced on watching the subsequent development of some of these children. That a profound disturbance of the central nervous system, as described by Spiller[4] and shown in cerebral diplegia and mental deficiency, may result is accepted, and has happened in one of my cases. That there may be a less severe disturbance, and one from which recovery may take place, is suggested by the extreme muscular atony which occurred in another of my cases. This was a striking feature at age eleven months and a few months later great improvement was reported. It seems possible that osseous dystrophy may be another direct sequel.

That calcium metabolism is disturbed in jaundice has been shown by many workers (reviewed by Ivy[5]), although they are not in agreement as to the mode or type of disturbance. In relation to the case under consideration, the work of Buchbinder and Kern[6] is of most interest. They have shown that the age factor is all important in determining the changes in blood calcium in obstructive jaundice. Puppies showed a definite decrease in serum calcium and disturbance of bony structure, whereas little or no disturbance occurred in adult dogs. In puppies, they produced jaundice by ligaturing the common bile-duct. Between the 20th and the 60th days there was a fall in the blood calcium. During this time there was skeletal growth. At 20 days there were no bone changes but after 60 to 70 days there was 'a high grade rarefaction, cortical thinning with relatively wide medullary spaces and a lack of contrast generally . . . One animal developed bilateral cysts in the bones.' They also produced evidence to show that there is some alteration of the parathyroid function in obstructive jaundice in animals. The disturbance produced by thyro-parathyroidectomy is much less severe in chronically jaundiced animals, and tetany does not appear in late obstructive jaundice in puppies in which the serum calcium has fallen to the tetany level.

In bile-fistula dogs, that is in dogs in which the bile is prevented from entering the intestine but in which the liver itself is not injured, Whipple[7] has shown that bony abnormalities develop, but can be cured or prevented by feeding with whole liver.

These findings suggest that the altered calcium metabolism in obstructive jaundice in young animals depends on something other than mere absence of bile from the intestine and consequent diminished absorption of fat and calcium. It seems likely that the liver has some concern with calcium metabolism and therefore with normal growth of bone and nerve tissue; and it is accepted that pathological changes in bone and at least functional changes in the nervous system and extreme muscular atony do occur in different cases of rickets, and are all due to the same initial cause. What determines the predominance of one or other feature is not fully known, but Mellanby's[8] experimental work suggests a possible reason for the

FIG. 3.—Showing osteoporosis and spontaneous fracture in a case of kernicterus.

muscular atony. Under certain dietetic conditions Mellanby was able to produce in dogs a combination of severe inco-ordination and muscular weakness. The spinal cord in these animals showed in various tracts a scattered degeneration which he regarded as mainly due to an absence of vitamin A from the diet. Bone changes and nerve changes in rickets are due to lack of vitamins A and D. Harris[9] lays stress on the importance of A as well as D in normal ossification. It is not unlikely, then, that parallel conditions will ensue if the factor controlling the utilization of the vitamins is impaired or destroyed. The liver is the main storehouse of vitamins and presumably controls their optimum distribution and activity. This hypothetical special

function may well be affected in the profound disturbance of all liver functions in prolonged jaundice. The exact nature of the pathological changes in the central nervous system in icterus gravis is an open question, but it is possible that a common cause, common to them and to the pathological changes in the bones in this case, may be found in an impairment or destruction of a liver function concerned with the utilization of vitamins, particularly A and D. This may be allied to, or independent of, a failure of the liver to incorporate the vitamins, a failure which Green[10] has demonstrated in some puerperal cases.

The survival of infants suffering from icterus gravis has been rare until recently, and it is not surprising that I have failed to find a previous report of the combination of conditions here described, or a record of a case showing similar features in the bones. When I saw this child in 1928, I was unaware of the importance of pushing the treatment with adult serum or blood, and gave only sufficient to arrest the bleeding. That may explain the unusually long duration of the jaundice. Subsequent cases have been treated more generously, but one of them who also developed cerebral diplegia, showed a general osteoporosis and had a spontaneous fracture (Fig. 3).

Summary.

1. A case of osseous dystrophy following icterus gravis neonatorum is reported.

2. Work on experimentally jaundiced puppies producing similar bone changes is discussed.

3. A comparison is made between the bone and nerve changes in rickets, and the bone and nerve changes following icterus gravis neonatorum.

4. It is suggested that the liver not only stores vitamins but controls their distribution and activities in normal conditions.

5. This function may be impaired or destroyed in prolonged jaundice, and, occurring in infancy, a pathological condition of bones as well as of nervous tissue may ensue.

I am very much indebted to Dr. E. M. Hickmans for the biochemical reports, and to Dr. C. G. Teall, Radiologist to the Children's Hospital for making many X-ray examinations.

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RICKETS FOLLOWING AN ATTACK OF ACUTE NEPHRITIS

BY

E. A. COCKAYNE, M.D., F.R.C.P.,

and

F. P. LEE LANDER, M.R.C.P.

(From the Middlesex Hospital, London.)

Renal rickets, although a rare disease, has received an amount of attention in the literature out of proportion to its importance or the frequency of its occurrence. This undue prominence is probably on account of its bearing on infantile rickets, and also on the difficult problem of calcium and phosphorus metabolism.

It is not intended to give here a complete review of the literature, but to mention only those papers which deal with the clinical aspect of the disease, and then to discuss briefly some bio-chemical findings in the condition, and some hypotheses of the pathogenesis of the rickets.

Barber[1] in a series of papers gives the records of some 17 cases, which have been either under his care, or to which he has had direct clinical access. This is the largest series reported by one author. All Barber's patients were children under the age of 12, and in no case was a definite history of acute nephritis obtained. The children are presented on account of stunted growth, knock-knee, or excessive thirst with frequency of micturition.

Clinical examination provides remarkably little information. The cardio-vascular system is usually normal; there being no cardiac enlargement, a normal blood-pressure, usually no retinal changes, and no palpable thickening of the arteries. The skeleton may show deformities, either dwarfism or genu valgum being present. The urine is pale in colour, of low specific gravity, and usually shows a trace of albumin, though it may be albumin-free for many days at a time. The disease is chronic in its course, but ultimately the patient succumbs to renal insufficiency. Pathologically, the kidneys show changes which approximate to those found in senile arterio-sclerotic kidneys. In most cases the heart is of normal weight and the peripheral arteries are unchanged.

Parsons[2] discusses the disease mainly from the radiological and bio-chemical points of view, and comes to the conclusion that renal rickets is a low-calcium type of rickets. In order to explain the normal serum calcium which is frequently found in the condition, he postulates an over-action of

the parathyroids in the attempt on the part of the body to prevent the occurrence of tetany. Mitchell[3], in an exhaustive article, presents 200 cases of chronic renal disease in children collected from the literature. In only 76 of these was he able to find references to skeletal deformities, the majority of these 76 cases showing genu valgum. In only 2 of the cases collected by Mitchell was the renal lesion definitely secondary to acute nephritis. Both of these were reported by Brockman[4].

Case report.

The case reported below has several unusual features. The nephritis was secondary to an attack of acute nephritis, and the patient was under observation the whole time for nephritis. The rapidity of the advancement of the lesion and the early death of the patient, also constitute features absent from the common form of the disease.

R. W., male, aged 13 years, gave a history of chicken-pox and whooping-cough in infancy. He had attended hospital, at 7 years, on account of his mental condition, and a diagnosis of amentia was made. Unfortunately there is no record of an examination of the urine. Wassermann reaction was negative.

In March, 1928, the patient, then 10 years old, was admitted to the Hospital for Sick Children, Great Ormond Street, suffering from œdema of the face and legs, and marked hæmaturia.

On examination the patient was found to be a well-developed boy of a sullen backward disposition. Œdema of the face was so great that he was unable to open his eyes. The chest, abdominal wall, and legs were very œdematous. Ascites was present, and also small bilateral pleural effusions. The heart's apex-beat was ½-in. outside the nipple line. Blood pressure = 150/90. The urine showed a sp. gr. 1025, with albumin 1·2 grm. per litre. The blood urea = 54 mgrm. per 100 c.cm., and the blood cholesterol = 325 mgrm. per litre. His weight was 87 lb.

From admission the condition of the patient gradually improved. The œdema disappeared within six weeks, the blood pressure fell to 100/70, but the nitrogen retention persisted throughout the patient's stay in hospital. The daily output of urine varied between 10 and 45 oz., with a daily average of 26 oz.

In June, 1928, the ascites and pleural effusions were still present. An examination of the blood gave the following values:—urea, 59 mgrm. per 100 c.cm.; cholesterol, 338 mgrm. per 100 c.cm.; serum calcium, 7·7 mgrm. per 100 c.cm. The patient was discharged at the end of July, 1928, to a convalescent home.

He next attended the hospital in January, 1929, as an out-patient. He was found to have œdema of the face and legs. The urine was of sp. gr. 1002, with a heavy cloud of albumin, but no blood. Weight, 79 lb. The boy attended regularly at monthly intervals until January, 1930. After the first examination, the urine never contained more than a trace of albumin, and the œdema was confined to the lower part of the legs.

From January, 1930, the patient attended as an out-patient at the Middlesex Hospital, and was seen every month until September, 1931. During this period the amount of albumin in the urine gradually increased, but the œdema remained unobtrusive. In September it was noticed that the patient had developed genu valgum, which, his mother said, had been present for about six weeks. The patient

was recommended for admission, and came into hospital early in October, when his condition was found to be as follows:—The heart's apex-beat was outside the nipple line in the fifth space. The aortic second sound was accentuated. Blood pressure = 140/105. There was no œdema and no ascites.

There was marked genu valgum. No other clinical evidence of skeletal deformity could be found.

The retinæ showed blurring of the optic discs with exudates, but no hæmorrhages.

The patient felt quite well, and did not suffer from headaches and did not vomit.

Blood analysis on admission:—urea, 100 mgrm. per 100 c.cm.; non-protein nitrogen, 66 mgrm.; serum calcium, 7·5 mgrm.; phosphates, 9·8 mgrm.

The urine was of sp. gr. 1010. Albumin = 4 grm. per litre.

X-ray examination showed typical rickety changes at the knee- and wrist-joints.

After seventeen days stay in hospital, the patient's condition became suddenly worse. He developed intractable vomiting and a very severe headache. Two days later he became comatose, with fine muscular twitchings, and died.

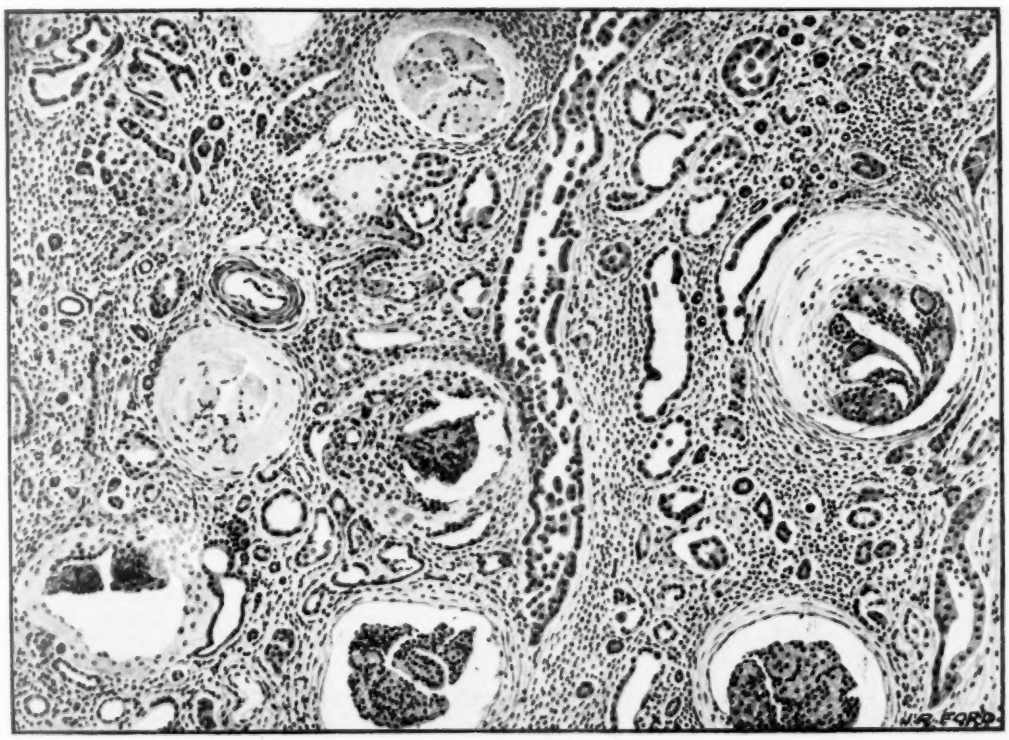

FIG. 1.—Section of kidney (× 125).

Post-mortem examination.—KIDNEYS. Macroscopically, both kidneys were smaller than normal and pale in colour, the capsules stripped with difficulty leaving a granular surface. On section the cortices were narrowed with complete loss of the cortical pattern.

Microscopically, the kidney showed considerable disorganization, most of the glomeruli being affected. Large numbers of glomeruli were completely fibrosed, and of the remainder many showed proliferative glomerulitis and capsulitis of varying degree: a few showed ischæmic changes. The secreting tubules were dilated, with degeneration and thinning of the epithelium; many contained hyaline and finely

granular casts. The interstitial tissue was greatly increased in amount and contained numerous foci of chronic inflammatory cells.

BONES. The gross deformities have already been described. Section of the bones showed them to be softer than normal with broad and irregular epiphyseal lines.

Microscopically, the general appearances were those of true rickets. The epiphyseal cartilages were thickened with increase of the zone of proliferating cartilage; the vascular invasion of this zone was irregular leaving islets of unchanged cartilage on the metaphyseal side. An excessive amount of osteoid tissue was

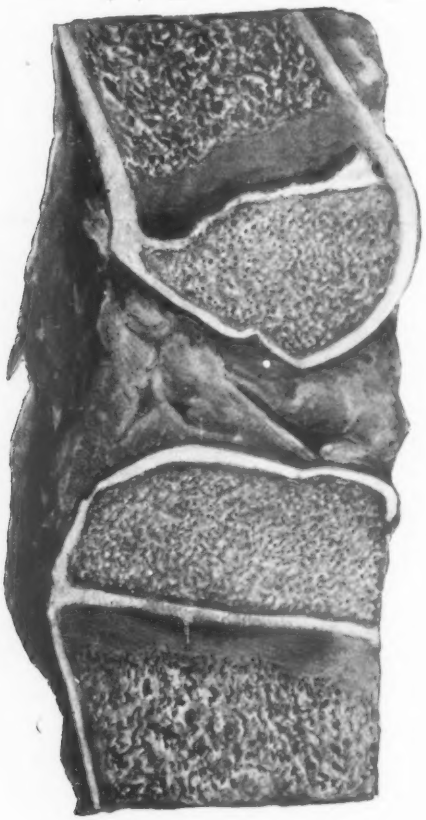

FIG. 2.—Section of knee-joint.

present and there was no hæmatogenous marrow for a considerable distance up the shafts, the marrow spaces being occupied by fine fibrillar connective tissue.

OTHER ORGANS. Except for some hypertrophy of the left ventricle nothing relevant was found.

SUMMARY. The post-mortem findings are therefore those of chronic glomerulo-tubular nephritis with left ventricular hypertrophy, accompanied by bony changes resembling those of true rickets.

Discussion.

The outstanding feature of the case is the rapidity with which the disease passed through all its phases to a fatal issue. The patient developed acute

nephritis in March, 1928; in April and the following months, the subacute phrase of the disease had set in; genu valgum appeared in September, 1931, when the disease had reached the chronic phase; and death occurred in November, 1931, about 3½ years after the initial attack.

From a study of this case, it is seen that bony changes occur in chronic renal disease of inflammatory origin, as well as in renal disease of doubtful, and probably degenerative, origin of childhood. The bony changes are the result of the disturbances in calcium and phosphorus metabolism. Hess[5] states that the earliest change in true rickets is a rise in the phosphate level in the blood, and in this case the blood phosphate value (in one isolated finding) was markedly above normal, three years before bone changes became manifest.

Mitchell[3] advances the hypothesis that the bony changes are due to a calcium deprivation, which is secondary to retention of phosphates by the kidneys. He states that there is a greatly increased excretion of phosphates by the bowel, and this interferes with calcium absorption by forming insoluble calcium phosphates, which are excreted, as such, in the fæces. In the light of our present knowledge this is unlikely, as calcium and phosphorus are thought to be absorbed in the small intestine and are both excreted at a lower level. Thus at the site of calcium absorption, the phosphorus concentration in the bowel should be normal.

Various authors have objected to the identification of the skeletal changes in renal rickets with those of true rickets, not so much because the pathological picture varies from that found in true rickets, but because the phosphate-calcium ratio is usually above 40, and in true rickets it is always found to be below this figure. This reasoning is unsound, because it is attempting to fit the facts of the problem to a particular hypothesis, and not, as it should be, formulating an hypothesis to fit the known facts.

In an unpublished case, one of us (E.A.C.) has noted a greatly increased phosphatase in the blood, and this would correspond with the raised level found in true rickets. The significance of the blood phosphatase is as yet imperfectly understood, so it would be meaningless to attempt to build arguments on this finding.

Treatment is directed solely against the nephritis, and as would be expected, no drug or diet influences the course of the disease. The inevitable end may be hastened by operative interference to the genu valgum, and this has happened in a number of instances, in which, at the time of examination, albuminuria was absent.

We wish to acknowledge our indebtedness to Dr. Robert Hutchison for allowing us the use of his ward notes. Also we wish to thank the director of the Bland-Sutton Institute of Pathology for putting at our disposal the pathological data; and the professor of the Courtauld Institute of Biochemistry, and Dr. Payne, for the figures relating to the blood chemistry.

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OBSERVATIONS ON DYSENTERY IN CHILDREN

BY

DAVID NABARRO, M.D., F.R.C.P.,

and

A. GORDON SIGNY, M.B., B.S.

(From the Hospital for Sick Children, Great Ormond Street, London.)

For more than 20 years one of us (D. N.) has been interested in the subject of bacterial dysentery in this country, and many years ago came to the conclusion that the disease was much more prevalent among children than was generally realized. As far back as 1914, in a short paper written in conjunction with A. Distaso[1], it was shown that in 19 cases of enteritis and colitis and 2 of cœliac disease, all in children, a probable dysenteric infection could be demonstrated by the isolation of a Flexner-type dysentery bacillus from the fæces in 5 cases, and by the agglutination power of the patient's serum in all the cases. The Sonne bacillus was not identified as we were unacquainted with it at that time.

The relation of the dysentery bacilli to the zymotic enteritis or epidemic diarrhœa of infants is an interesting problem which is still in part unsolved. In 1902, Duval and Bassett[2] isolated dysentery bacilli from 42 out of 53 cases of infantile diarrhœa, and they concluded that the dysentery bacillus ' is an important, if not the most important, cause of summer diarrhœa in children.' In 1903, the Rockefeller Institute undertook a comprehensive investigation in several American cities on the occurrence of the dysentery bacillus in the summer diarrhœa and other diarrhœal diseases of children. Dysentery bacilli were isolated in 63·2 per cent. of the 412 cases investigated; they were mainly of the Flexner type, but the Shiga bacillus was also met and occasionally the two types were associated. Flexner[2], who had charge of the investigations, in his conclusions stated ' that it is probable, though not proven, that the B. dysenteriæ appears at times among the saprophytic bacteria of the intestinal contents.'

Since 1913 a number of cases of dysentery have been recognized every year in this hospital, but owing to the fact that prior to 1912 no systematic investigation for dysentery bacilli in the fæces was carried out, it is impossible to say if the numbers have increased since the war.

In the diarrhœa epidemic of 1921 when 111 cases of summer diarrhœa were admitted to the Hospital for Sick Children, Great Ormond Street, bacteriological investigations were carried out by one of us (D. N.) in

co-operation with D. Paterson[3] upon 68 of these cases. Dysentery bacilli of the Flexner and Sonne types were isolated in 27 out of the 68 cases studied (39·7 per cent.), and in 11 out of a further 39 ' sporadic ' cases of diarrhœa in children and nurses. The Sonne bacillus was not recognized as such at the time, but the organism isolated was called the B. coli anærogenes[3].

Present investigations.

The subject matter of the present paper is based on all the cases of dysentery which occurred in the hospital during 1929, 1930, 1931, and the first 11 months of 1932. Most of the cases, it will be shown, occurred in small ward outbreaks, and it will be seen that the number of established cases, i.e., bacteriologically proven, is far greater than would be expected from current opinion as to the prevalence of the disease in this country. Dysentery in England is regarded as a rare disease outside mental hospitals, and acute attacks of diarrhœa in children are labelled gastro-enteritis or ileo-colitis, often without any attempt being made to establish a bacteriological diagnosis.

Bacteriology.—Routine examination. It is now a routine of this hospital that every case of diarrhœa admitted to the wards, or arising during a stay in hospital, is immediately placed under infectious precautions and a stool sent for bacteriological investigation. Whether the result is positive or negative, the child is only removed from these precautions when the stool shows no abnormal micro-organisms on at least three consecutive days. Routine stool examinations consist of careful macroscopic and microscopic search for blood and pus, and of cultural investigations. The latter are made straight from an emulsion of the fæces, preferably using a portion containing mucus, on two McConkey plates, and after 24 hours' incubation every type of non-lactose fermenting colony is further investigated. The number of non-lactose fermenting colonies which are isolated from an acute dysenteric stool varies enormously, from one or two colonies per plate to pure growths. The diagnosis of the type of micro-organism is determined and controlled by the following two methods:—

By direct agglutination:—Rabbit serum of high agglutinating titre is prepared by 3 or 4 weekly intravenous injections of formalized broth cultures of the commonest strains (Flexner V, W, X, Y, Z and Sonne). The sera are then ' absorbed ' with all the other strains to remove the co-agglutinins, and are used at 1/10 or 1/20 dilution for rapid diagnosis. One drop of each serum is placed on a clear slide, and mixed with a small part of the non-lactose-fermenting colony. After gently rocking the slide, the result is rapidly obvious, for the micro-organism is clumped by its corresponding serum very markedly, and not affected by any of the other sera. The result is easily read by the naked eye. By this means it is possible to label a case of acute diarrhœa as dysentery Flexner Z or dysentery Sonne, etc., within 18 hours of the onset of the diarrhœa. It is essential to have reliable sera.

Secondly, more detailed examination of the micro-organism is usually required, although in very few cases have we come across disagreement between the ' rapid ' and the more laborious methods. The colony to be investigated is picked off, grown in 1 per cent. peptone water for 6 hours, its motility examined, and then one or two drops of this culture are transferred to a series of carbohydrates for fermentation reactions. We use for routine purposes the following sugars:—Glucose, mannite, dulcite, lactose, saccharose, salicin, maltose, phenol red milk, and lactose gelatine. The Flexner sugar reactions, widely known, are normally the production of acid without gas formation in glucose, mannite, maltose and milk; the milk later turning alkaline. It is, of course, a non-motile gram-negative bacillus, and produces a variable amount of indol.

The reactions of the Sonne bacillus are less generally recognized. They consist of acid without gas formation in glucose, mannite, maltose, and milk, in 24 hours. Lactose is nearly always fermented, but this is a much slower process than with the other sugars, varying from 1 to 14 days. The milk remains acid throughout, and occasionally may be clotted. The reaction upon saccharose is variable, the sugar being sometimes fermented by Sonne and sometimes not. As a rule there is no production of indol, but an occasional indol-producer may be met.

Blood agglutination.—The majority of the cases of dysentery in these four years have been bled at least once, and their serum used for agglutination tests. Fifty control cases were also studied. Dreyer's method was used, and the antigens were Oxford standard agglutinable cultures, various stock strains of Sonne cultures, and when possible the patient's own culture. The results were of great interest, and we hope to make these, together with a full discussion on the bacteriology, the basis of a future paper. It will be sufficient here to say that we consider a ' standard ' agglutination with any of the dysentery strains to a titre of 1/125, or a *strong* agglutination even at 1/50, as presumptive evidence of a recent dysentery infection. We would also point out here the necessity of utilizing more than one strain of the Sonne bacillus for agglutinable cultures, as there is no doubt that many positive reactions are missed by not using representative mixed strains.

Symptomatology.—The clinical picture of the disease in most of the cases here recorded was abdominal pain followed by severe diarrhœa, usually associated with the passing of a fair amount of blood and mucus. The early dysenteric stool, in fact, is very typical, containing practically no fæcal material at all. There is a fair amount of tenesmus, and the child then passes a small quantity of blood and mucus. As many as six to ten motions may be passed during the day, and this diarrhœa is usually followed by constipation lasting one or two days. At the onset there is a good deal of malaise, irritability, sometimes vomiting, and in most cases a varying degree of temperature, 100° to 103°, which symptoms may last only one day. Older children are rarely gravely affected, but whilst the diarrhœa lasts they may complain of thirst. In very young children the diarrhœa may be of a mild

character, so much so that it may be considered unnecessary to make a bacteriological investigation or to regard the child as really at all seriously ill. All degrees of severity are met, however, from this mild type to the severest of all, when a young baby, usually under six months of age, is infected. The child passes blood and mucus six to eight times in one day, becomes rapidly dehydrated and collapsed, and may then die in a condition of severe toxæmia. The varying types that may be met have been well described by Paterson[3] in the paper already referred to.

In some of the milder types, the associated abdominal pain, with the passage of blood and mucus has simulated very closely the picture of acute intussusception.

Treatment.—Taking general measures first, all patients must be treated as highly infectious, and should be nursed with most careful precautions to prevent spread. It is obvious that if a child passes as many as 10 stools in one day, and is handled by 3 or 4 nurses, the chances of spreading the infection are greatly multiplied. We would strongly urge that no nurse who is detailed to handle the stools of a dysentery patient be allowed to touch the food of any other patient. We are convinced that this is the most common mode of spreading the infection. The children have quite marked tenesmus, and but little control over these early very loose stools, and so the call for the bed pan should be quickly answered, or the bed clothes will have to be changed very often. They have very poor appetites during the acute stages, and will eat very little more than milk or pudding.

As regards medicinal treatment two modes of action may be adopted, either an attempt to clear the bowel of its noxious contents quickly by means of aperients, or an endeavour to stop the diarrhœa, with its depleting effects, by means of bismuth. We have had no particular preference for either method of treatment, and cannot say that either gives better results than the other. The children appear to improve in any case.

SPECIFIC THERAPY.—(a) Bacteriophage. We have tried d'Herelle's dysentery-phage in the treatment of a few of the cases. This is prepared from a mixed culture, but does not contain any Sonne-phage. The results on the whole were disappointing, and as the children must be practically starved for 24 hours during the treatment, we no longer use it and do not feel justified in recommending its use.

(b) Serum therapy. Here, too, we have not had encouraging results. The most satisfactory of the sera appears to be the Lister anti-dysentery serum, which is mixed, and contains some Sonne antibodies. We feel bound to say in extenuation of these apparently unsatisfactory results of specific therapy, that they were not tried in the 1929 cases, and since then practically all the cases have been Sonne infections in older children, and have begun to show signs of recovery within 24 hours, before any particular treatment was adopted. If, however, a child is obviously acutely toxæmic, we would recommend the immediate administration of the serum, in doses of 10 c.cm. intramuscularly, repeated if necessary every 24 hours.

TABLE 1.

SUMMARY OF 106 CASES IN 4 YEARS.

	Sonne	Flexner Z	Flexner W
1930	19 + 1 nurse	15 + 1 nurse	0
1929	0	1	0
1931	25 + 1 nurse	1	1
1932 (11 months)	38 + 3 nurses	0	0
Totai	82 + 5 nurses	17 + 1 nurse	1

Incidence.—It will be seen in Table 1 how the incidence of dysentery varies in this hospital. Of a total of 106 cases of dysentery over a period of 4 years, there were 18 cases of Flexner Z, and 16 of these occurred in 1929. Sonne infections are more evenly spread, except in 1930, when there was not even one case. All these cases were bacteriologically proven by isolating the micro-organisms from the stools. There were several cases of undoubted dysentery, not bacteriologically proven and therefore omitted from this paper, which were the obvious starting point of an epidemic, and the agglutination reactions of their blood proved to our satisfaction the true nature of their infection.

A severe ward outbreak at the end of 1928 induced us to investigate fully every case of diarrhœa occurring in the hospital. Until that time the importance of the immediate bacteriological examination of all abnormal stools, particularly those showing blood and mucus, was not recognized in the wards. We give here a short summary of the worst of the epidemics of 1929.

1. The first cases investigated were the members of one family. In this family a boy, aged 1 year and 11 months, was taken ill with acute diarrhœa at a convalescent home early in January, 1929. On the 17th he returned home, and within 3 days, 4 other members of the family became severely ill with acute diarrhœa, the eldest, aged 8 years, dying within 14 hours of the onset of the diarrhœa. Two of the children came into hospital, and made good recoveries. Flexner Z was the causal micro-organism, and it was recovered from the stools of the first case and from one of the brothers. A coroner's inquest was held on the child that died, and a verdict of death from 'acute food poisoning' was returned, because there was no bacteriological examination made of the bowel. In March, Flexner Z was still isolated from the stools of the original case, and his blood agglutinated Oxford V and Z, but stronger with Z.

2. (Medical Ward A.) L. N., aged 1 year and 2 months, had erysipelas of the thigh for which he was admitted to another hospital. He had slight diarrhœa when admitted there just before Christmas, 1928. On the 17th January, 1929, he was admitted into this hospital markedly collapsed (temperature 96°), and he had 1 stool that day. Next day his temperature rose to 100° and he passed 9 stools which were green, with some blood and mucus. He went on passing 7 to 10 stools per day until his death on the 23rd January. None of these stools was examined bacteriologically. At the post-mortem examination the bowel was 'flannel-like' and injected, but there was no true ulceration and no dysentery bacilli were isolated from the inflamed areas. The heart's blood agglutinated well with Oxford Flexner Z and Sonne.

Following this, on the 20th January, 1929, another child aged 6 weeks, who had been in hospital since the 15th December, 1928, for vomiting, and had made a good recovery, developed an acute diarrhœa, with a temperature of 102°. Eight stools were passed that day, and thereafter an average of 7 stools per day until death on 29th January. The temperature chart in this case was of interest, there

being a slow daily decline from 102·4° on the 22nd January to 95° on the 28th, the day before death. Flexner Z was isolated from the stools in this case during life, but the bowel, post mortem, although showing typical dysenteric lesions, yielded no dysentery organisms on culture.

On the 22nd January, 1929, a nurse who had had charge of both these cases was taken ill with acute diarrhœa and Flexner Z was isolated repeatedly from her stools. Her blood on the 29th January agglutinated well with the dysentery bacilli but best with Flexner Z.

3. (Surgical Ward A.) S. H., aged 6 months, was admitted on January 17th, 1929, with blood and mucus in his stools under the diagnosis of recurrent intussusception. During the previous 2 days he had been passing a slight amount of blood and mucus. On admission the child showed no physical signs and the stools were normal. On 23rd the temperature began to rise, reaching 102° on the 27th. The stools simultaneously increased to 3—5 per day, and the child died on February 7th with a temperature of 103°. No stools were sent for investigation during life, and post mortem no obvious dysenteric lesions were detected, and as dysentery was not suspected no bacteriological examination was made.

Following this case between the 6th and 20th February 6 other children, the majority of whom had been in hospital for some time, suddenly developed acute diarrhœa of a severe type. Three of these children were under 2 years of age and died; 1 aged 3 and the other 2 aged 10 recovered. B. Sonne was isolated from each of these cases: in the 3 that recovered it was found in the fæces; in 2 of those that died it was found in post-mortem lesions of the bowels; and in the third of the fatal cases it was recovered from the fæces during life but not from the bowel post mortem.

4. (Surgical Ward B.) A. H., aged 7½ years was admitted on October 5th, 1929, for tonsillectomy. She had slight pyrexia 100° and loose motions on admission. On the 6th she had 3 watery stools with blood and mucus, but notwithstanding this she was allowed up and played with other children in the ward. On the 7th B. Sonne was isolated from her stools. Her temperature was normal throughout and the patient became a convalescent carrier, the micro-organisms being isolated over a month later.

In connection with this case 3 children in the ward developed diarrhœa with blood and mucus, and from each one the Sonne bacillus was isolated. All made uninterrupted recoveries.

5. (Medical Ward B.) M. W., aged 3 years, was admitted for pains in the stomach, vomiting and severe diarrhœa with a good deal of blood and mucus. This had started on the 3rd October, and she was admitted on the 4th with a temperature of 101°. She passed 10 stools on the first day, then 6, 5, 4 and 1 on consecutive days. Flexner Z was isolated from the stools, and anti-dysenteric serum was given in 10 c.cm. doses daily for 4 days. The temperature was normal by the 9th, and the patient was discharged as fit on the 16th October.

Following on this case there were 5 cases of dysentery in this ward. The first of these cases started on the 27th October, i.e., eleven days after the child M. W. had been discharged, and the last one to occur was in a child aged 4 months, who had been admitted for feeding difficulties and anæmia, and who had been doing well until he started an acute diarrhœa on the 12th November, from which he died on the 20th. In all these cases Flexner Z was isolated from the stools.

In the later years early examination of suspected stools has often put us on guard against the spread of infection, but even so we have had many small epidemics, usually affecting 4 to 8 children in one ward before it is properly stamped out. The earlier recognition of cases has, however, diminished the number of contact cases as, for example, in one ward where 4 cases of dysentery were admitted in 1932 and there followed only 1 contact case.

TABLE 2.

AGE AND MORTALITY INCIDENCES.

	1929		1930		1931		1932 (11 mo.)	
	Flexner	Sonne	Flexner	Sonne	Flexner	Sonne	Flexner	Sonne
Under 1 year ...	3 (2)	4 (3)	0	0	0	1	0	1
1–2 years	4	2 (1)	0	0	0	1	0	10
2–5 years	4	5	0	0	0	10	0	10
5–12 years ...	4	8	1 z	0	1z—1w	14	0	17
Nurses	1	1	0	0	0	1	0	3
Totals ...	16 (2)	20 (4)	1	0	2	27	0	41

The numbers of fatal cases are given in brackets.

Age and mortality incidences.—From Table 2 it can be seen that all the deaths occurred in 1929. All of these were under 2 years of age, and of the total of 6 fatal cases, 4 were from Sonne and 2 were from Flexner Z infections. The total death rate over the 4 years, however, is very much more favourable in Sonne infections, being only 4 out of 88 cases (4·5 per cent.), whereas with Flexner infections there were 2 deaths out of 19 cases—really too few from which to draw conclusions, but nevertheless giving a death rate of 10·5 per cent., or more than double the Sonne rate.

The mode of infection is important from the statistical point of view. In 1929 there were 15 cases infected outside the hospital, and these gave rise to 21 cases after admission. In 1930 the only case of the year was admitted for its dysentery. In 1931, of the 29 cases, 11 were admitted, and 18 contracted in hospital. 1932 shows 13 cases admitted, giving rise to 28 cases contracting dysentery in hospital.

Discussion.

The object of this paper is to draw the attention of pædiatricians to the frequent occurrence of bacteriological dysentery in institutions in which children are cared for. Our experience in this hospital is almost certainly not unique, for we know that several children's hospitals in London[4] and the provinces[5, 6, 7] have similar outbreaks. Reports from various Continental countries[8, 9], Australia[10], Canada[11, 12], India[13], and the United States of America[14] show also that similar outbreaks of dysentery occur in those countries.

Our investigations lead us to conclude that the commonest infecting micro-organism is the Sonne bacillus, and we may add that we very rarely indeed come across Morgan's No. 1 bacillus, which for some years was regarded as a likely cause of epidemic diarrhœa. Even to this day the Sonne bacillus is by most clinicians and pædiatricians regarded as of little practical importance, but it should be recognized that in very young children it may produce fatal infections. The ultimate effects of the dysentery bacillus are not known, but it is possible that cases of arthritis, malnutrition and even cœliac disease may be numbered amongst them, and the positive blood agglutinations which have sometimes been found associated with these

clinical conditions, may indicate that the disease may be an ætiological factor.

Several of our cases have become convalescent carriers, harbouring the micro-organism for months after the attack, without apparently any ill effects after the first symptoms had subsided. They are the probable sources of infection in most outbreaks. The infection spreads rapidly amongst children living together, and too great stress cannot be laid upon the adoption of stringent precautions to prevent this spread.

Treatment in these cases is rather unsatisfactory, because it is apparently unnecessary to interfere in most of them. Nevertheless, with the ordinary means of treatment employed, relapses sometimes occur, and it is quite possible that treatment with anti-dysenteric serum in a severe case might prevent such relapses. It certainly holds out the greatest hope in the case of an infant who is severely affected, if administered together with bismuth to combat the diarrhœa.

Summary.

1. The incidence of dysentery from the Flexner and Sonne bacilli is given in a children's hospital, over a period of 4 years, totalling 106 cases.

2. Deaths are recorded in 4·5 per cent. of Sonne infections and 10·5 per cent. of Flexner infections; but in the majority of cases, particularly in older children, the disease is mild.

3. The bacteriology of the fæces and the blood agglutinations are briefly discussed, and the importance of the latter emphasized.

4. Suggestions are put forward for minimizing the risk of spread in institutions.

We wish to thank the Honorary Staff of the hospital for permission to use the material under their care.

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OVARIAN SARCOMA IN CHILDREN

BY

ROBERT GITTINS, M.D., M.R.C.P., D.T.M. & H.,

and

J. C. HAWKSLEY, M.D., M.R.C.P.

(From the Children's Hospital, Birmingham.)

In a communication shortly to be published* we are recording a case of bilateral ovarian neoplasms in an infant with generalized reticulo-endotheliosis and monocytic leukæmia. The histology of the ovaries showed the tumours to be endotheliomata. The following were the chief features of this case.

M. D., aged 1 year, was admitted for wasting, under Dr. Smellie, to the Birmingham Children's Hospital. Bilateral, smooth, freely movable tumours, the size of cocoanuts, were discovered occupying the iliac fossæ, and regarded as ovarian sarcomata. There were no general signs of ovarian dysfunction. The tumours were removed by Mr. Scott Mason. After initial improvement the child's condition began to deteriorate, and metastases were suspected. A blood count just before death revealed leukæmia of histiocytic type. No metastases were found at autopsy, but widespread reticulo-endotheliosis was found. Re-examination of the ovarian tumours revealed a reticulo-endotheliomatous structure. The case was therefore one of bilateral ovarian endothelioma with generalized reticulo-endotheliomatosis and monocytic (histiocytic) leukæmia.

We have been unable to find any other precisely similar case in the literature. We have, therefore, taken the opportunity of reviewing the literature of ovarian sarcoma in infancy, excluding our own case in the category of this disease in enumerating the cases up to date. So closely do such rare tumours as endotheliomata mimic sarcomata that clinical differentiation appears to be impossible, while, though histological differences are present, these are so relatively slight that such processes have been termed reticulum sarcomata by some observers. Owing to these closely similar clinical and pathological features, it appears advisable at present to consider them within the classification of ovarian sarcomata for clinical purposes.

Clinical manifestations.—The clinical manifestations of ovarian sarcoma in children can with advantage be discussed under the following four headings:—

1. Changes due to presence of the tumour.
2. Changes due to the toxic effects of the tumour.
3. Changes due to disturbances of endocrine balance.
4. Changes due to metastasis.

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* *J. Path. and Bact.*, Edinburgh, 1933, January.

1. The commonest manifestation in ovarian sarcoma in children is the actual presence of an abdominal or abdomino-pelvic mass. The presence of this mass may be discovered accidentally by doctor, parents or child, it may cause local prominence of the overlying abdominal wall, or it may be first looked for owing to the occurrence of pain, either within the tumour or from the interference with neighbouring structures. When felt it is as a rule freely movable and situated in the lower abdomen on one side or the other, or in bilateral cases both sides. The surface is as a rule slightly nodular. Tenderness of the mass may be apparent; a number of the cases showing this have undergone softening or become twisted. Free fluid within the peritoneal cavity is commonly found. Cases are on record in which the tumour has been large enough to cause respiratory embarrassment and cyanosis, while at a late stage the mass may be more or less fixed by infiltration of its surroundings. In a few cases an antecedent history of a blow has been noted. Scheffey[1] questions if this was the cause rather than the means of bringing the child under observation. In one case recorded by Koster[2] the tumour had ruptured, and pieces were found lying free within the peritoneal cavity.

Interference with the other abdominal organs has often been noted, resulting in diarrhœa, constipation, vomiting, urinary disturbance and acute intestinal obstruction, for which latter condition more than one case has been operated upon.

By examination per rectum the tumour can often be felt bimanually, and a vaginal examination will sometimes reveal its attachment to the adnexa.

2. As in other malignant tumours, certain constitutional disturbances are apt to occur in this condition. Amongst those most commonly recorded are variable degrees of rise in temperature, listlessness, irritability and thirst. A secondary anæmia is often present. Changes in the leukocyte count are less constant. One case recorded by Bushnell[3] suffered from epistaxis and purpura, and showed a lymphocytic count which made him regard the case as one of lymphocytic leukæmia.

3. Of great interest and diagnostic importance, are signs of disturbance of the endocrine balance. Two definite types are recorded, one of sexual precocity, and the other of a failure to mature of the sex organs. The former, as would be anticipated, is found before the usual onset of puberty, and the latter after. Sexual hyperfunction is shown by a combination of the following signs:—Precocious menstruation, enlargement of the breasts, development of pubic and axillary hair, alteration in voice (only one case recorded), precocious development of the external genitalia, and enlargement of the uterus. These symptoms may all be found in tumours of the ovary apart from sarcoma, and also in tumours of other organs such as the pituitary body, pineal body and suprarenal glands. In cases associated with delayed puberty the menstrual function is delayed or absent, the secondary sexual characteristics fail to develop, growth is often retarded and mental development impaired.

4. Metastases are as a rule relatively late manifestations and may occur either by lymphatic spread, through the blood-stream, or by being scattered over the peritoneal cavity.

Our case of bilateral ovarian endotheliomata had but one definite sign, the most common; namely, the presence of freely movable tumours on each side in the pelvis and lower abdomen. These were accompanied by anorexia and irritability, and with anæmia which later developed into leukæmia.

Recorded cases.—The youngest recorded case of sarcoma of the ovary was found by Doran[4] in a premature infant born after seven months' gestation, who lived only a few minutes after birth. The condition was bilateral. Scheffey[1] has collected all the cases of ovarian sarcoma up to and including 20 years of age, to the year 1924. His total of 118 cases includes eight under the age of two, of which seven were unilateral and one (Doran's case) bilateral. Since his paper Bates and Sincerbeaux[5] have published a case of bilateral sarcoma of the ovary in an infant of ten months. We have not been able to trace any other cases under the age of two years, which leaves a total of ten cases, seven unilateral and three bilateral.

In order to bring Scheffey's list up to date we have collected all the published cases of ovarian sarcoma occurring under the age of 21 since his paper in 1925. These will be briefly discussed. They number 13 all told.

Cases 1, 2, 3, 4.—Four cases under the age of twenty-one years were published by Massazza[6] in 1925, with other cases in older women. The first was in a patient of 20 and was right-sided, the second in a woman of 19 was left-sided, the third was in a woman of 19 and was on the right side, whilst the fourth was on the right side of the patient, who was 19 years old. The fourth case seems to have been doubtful as its histology was suggestive of carcinoma.

Case 5.—This case published by Koster[2] in 1925 is the only instance recorded in which spontaneous rupture occurred.* Both ovaries were implicated and both had broken down, their pieces lying free in the peritoneal cavity. Secondary metastasis had occurred, and the patient went downhill rapidly after operation. No morbid histology is appended in the communication.

Case 6.—A girl of 15 years published in 1927 by Corlette[7].

Case 7.—Recorded by Atzerodt[8] in 1927. The tumour affected the right ovary and was present in a girl of 18 years.

Case 8.—Described by Southam[9] in 1928: was right-sided and occurred in a child of 2 years 10 months. Sexual precocity was a predominant feature.

Case 9.—Recorded by Brown and O'Keefe[10] in 1928. Bilateral ovarian lymphosarcoma in a girl of 16, with metastases in breast and gums.

Case 10.—Published by Wenger[11] in 1930 occurred in a child of two and half years.

Case 11.—Jaisohn's[12] case published in 1930. This occurred in a child of eight years and caused acute intestinal obstruction. The tumour was left-sided.

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* While in the press, another example of rupture of an ovarian sarcoma in a child has been privately communicated to us by Dr. Van Buuren and Dr. Naz. The case will be published by them later.

Case 12.—Recorded in 1931 by Bates and Sincerbeaux[5]. The right ovary was removed at operation. The patient, aged 10 months, succumbed and at autopsy the left ovary was also found to be sarcomatous.

Case 13.—Jivatoff, in 1927, published a case in a Russian journal, but we have been unable to trace a copy of it.

Age incidence.—Various authors have compiled statistical tables to demonstrate the incidence of sarcoma of the ovary. When compared with other tumours of this organ the condition is found to be relatively more common in childhood—in other words a higher percentage of ovarian tumours in childhood are sarcomatous. Bland Sutton[13] recorded 60 cases of ovarian growths in children under 15 years of age; of these 26·6 per cent. were sarcomatous. Hubert[14] recorded 195 cases of ovarian tumour up to 15 years of age; 18·3 per cent. of these were sarcoma. Wiel[15] gives 25 per cent. as his figure for ovarian sarcoma in 60 cases of ovarian tumour in children under 10 years old. Scheffey, in his paper already quoted, analyzed the available literature up to 1925 and found the highest age incidence to be between 21 and 30 years.

CHART I.

FREQUENCY OF OVARIAN SARCOMA UP TO 20 YEARS OF AGE.

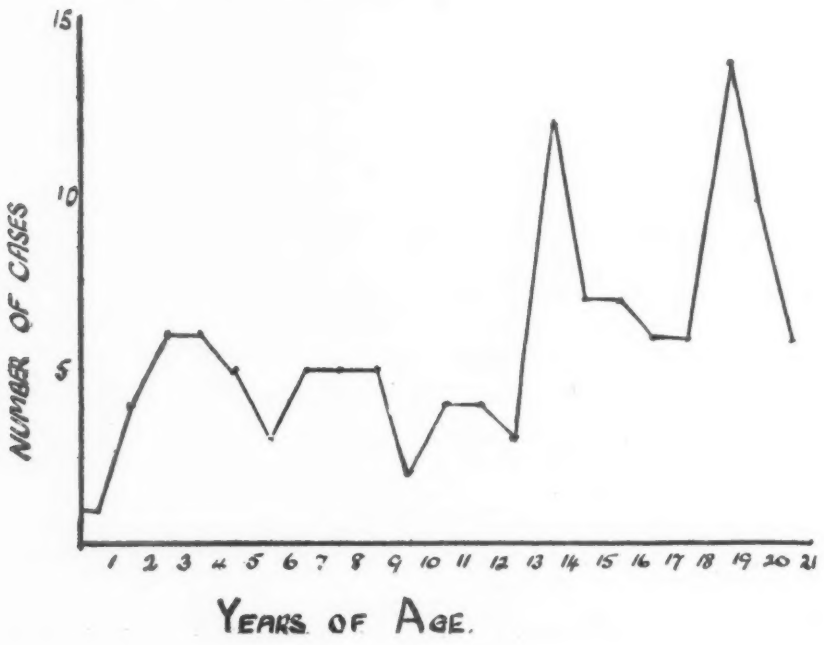

Chart I shows the age incidence of ovarian sarcoma according to the available statistics up to 20 years of age. There must be very many unpublished cases, but from the evidence of those available, there would appear to be a rise in frequency after puberty. In a few of the records the ages are not stated, the cases merely being recorded as occurring in childhood.

Varieties.—Ewing[16] regards ovarian sarcoma as a comparatively rare tumour and quotes Kroemer that it accounts for 5 per cent. of all neoplasms of the ovary. There are several histological varieties; the round-cell type is rare and met with in young subjects; tumours may show spindle and larger cells, even with some alveolar arrangement. Several observers have recorded giant cells, as well as considerable variation in the size of cells (Atzerodt[8], Jaisohn[12]); Massazza[6] reported two cases of spindle-cell sarcoma, unusual in that no mitoses were found. Manzi[17] described a stroma of fine fibrils spreading into the parenchyma of the tumours from the larger blood vessels, but without any vascular endothelial or adventitial proliferation. Several of Massazza's cases showed large cells with such a distribution of the fine stroma that an alveolar arrangement was produced and carcinoma simulated; his fifth case appears from his description more likely to be a carcinoma.

Probably many tumours showing indifferent types of cells are teratomatous. Smith and Motley[18] described such a type occurring as bilateral tumours removed by operation from a child aged three; they foretold recurrence, which prophecy was fulfilled five months later, when abdominal masses had developed. Histologically there were solid masses of cells with practically no intercellular stroma, and in places remains of tubules; the cells were very immature and no outer cell wall could be made out. Their report is especially interesting in view of the authors' case (which showed monocytic leukæmia) as a blood count was done: there was no abnormality in the differential count.

Foerster[19] recorded a unilateral round-celled sarcoma in a child aged four and a half, in whom metastases occurred after operation. Southam's[9] patient, aged two years and ten months, showed a small round-cell sarcoma. Malins's[20] case was a cystic sarcoma in a girl aged nine. Page's[21] case of fibro-sarcoma in a child aged six recovered, after operation; he believed it to be the youngest case recovering after ovariotomy for sarcoma. Wenger[11] described his case as an adeno-sarcoma. Hayd's[22] report of a bilateral sarcoma in a child aged five years gave histological details: rather large round cells with deeply staining vesicular nuclei and many karyokinetic figures; great tendency to hæmorrhagic infiltrations and necrosis of cells; groups of cells separated by connective tissue stroma, with numerous large spindle cells scattered in the stroma. In Higgins's[23] three cases, round cells predominated, though there was some mixture of spindle cells; the ages of the patients were five, seven and ten years. The patient of Bates and Sincerbeaux[5] was almost of the same age as our case of ovarian endothelio-mata, and showed a spindle-celled sarcoma; death occurred in five days after operation.

Endothelioma of the ovary was first described by Leopold in 1874, who considered that it was probably derived from lymphatic endothelium. Pick recognizes three types: (1) whorls or rows of cells; (2) cell groups resembling adenoma and carcinoma; (3) diffuse masses resembling sarcoma. The

present authors' case fell into Class 3. A review of cases of ovarian endotheliomata, together with histological details will be included in their report. As previously recalled, ovarian endotheliomata are clinically indistinguishable from sarcomata and are differentiated only by histological details.

Blood changes.—Fortunately blood counts have been recorded in a few of these cases; these are interesting in view of the hæmatological importance of our case. P. Jaisohn's[1,2] patient was aged eight years, and showed round, spindle, large spheroidal and giant cells (vide Ewing); there was slight anæmia (red cells 3,670,000, hæmoglobin 68 per cent., white cells 9,850, with no abnormality differentially).

Bushnell's[3] most interesting case of a young woman, on the other hand, did show some disturbance in the differential white-cell count. This was a case of bilateral round-cell sarcoma; epistaxis and a purpuric rash were observed. The hæmoglobin was down to 50 per cent., red cells 2,976,000, white cells raised to 13,400; differentially there were 66·4 per cent. lymphocytes with 12·6 per cent. hyaline cells and 3·4 per cent. myelocytes. Bushnell concluded that the blood showed a leukæmia of mixed cell type; but, on account of the absence of any number of immature cells of the lymphoblast type and the well recognized occurrence of lymphatic cell reactions, we feel that this diagnosis, hæmatologically, is open to some doubt, though we admit that the occurrence of epistaxis and a purpuric rash is very strong clinical evidence in favour of it. This case resembles the authors' in being bilateral, in the lymphatic reaction, in an increase of monocytes; but differs from it in the age, in the occurrence of metastases, and in having a hæmoglobin content much higher than is usual in the later stages of leukæmia. Koster[2] records a white count with secondary anæmia. As far as we are aware, there is no other recorded case of ovarian sarcoma or endothelioma complicated by leukæmia, and the type of leukæmia renders it unique.

Summary.

1. The literature on ovarian sarcoma relating to cases occurring up to and including the age of 20 has been reviewed.

2. L. C. Scheffey collected in 1925 all the cases of ovarian sarcoma up to this age; his total was 118 cases.

3. Thirteen cases have been reported since the date of Scheffey's paper, and these have been briefly reviewed.

4. The clinical and histological features as revealed by all these cases have been set forth.

5. The frequency of ovarian sarcoma at different ages up to 21 has been graphically represented.

We have pleasure in thanking Dr. Smellie for permission to use the records of the case quoted, and the Librarian of the Royal Society of Medicine for valuable help with references.

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